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## EXPERIMENTAL HEART DISEASE \*

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ONE of the great developments in clinical medicine of the past twenty years is the distinction between attacks of angina pectoris and attacks of coronary thrombosis. Even as late as 1923, Sir James Mackenzie did not make clinical diagnoses of coronary thrombosis.

Dock in 1896 was perhaps the first to report an instance of coronary thrombosis diagnosed ante-mortem and proved at autopsy. Huchard in 1899, in a pathological study of 185 fatal cases of angina pectoris, paid close attention to the coronary artery and noted the frequency of coronary thrombosis. Krehl (1901) called attention to the possibility of recovery after an attack of coronary thrombosis and suggested that the symptoms would be much more likely to be severe if the vessels were occluded suddenly than when sclerosis of the coronary artery was more diffuse and gradual in its development.

Obratzow and Strascheski (1910) gave the first important description of the clinical features of coronary thrombosis and diagnosed two of the three cases published. They pointed out the different pathological, as well as clinical pictures which might result, depending upon the size of the involved coronary artery.

Herrick (1912) was one of the first to show that cases of myocardial infarction could be diagnosed clinically, and that all cases were not fatal. In 1912 he stressed the point that coronary thrombosis was a clinical entity, could be diagnosed during life, and that it was not necessarily fatal. Herrick (1918, 1919) again contributed to this subject and tried to stress the importance of coronary thrombosis as a clinical disease—and one which should be diagnosed. To him must be given the credit for popularizing the diagnosis of the clinical entity of coronary thrombosis on this continent.

From 1920 to 1926 and more recently 1932 to 1937, many excellent papers and books have been written on the clinical aspect of this condition;

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these publications have facilitated the diagnosis of coronary thrombosis (Pardee, 1920; Levine, 1929; Levy, 1929; White, 1931; Sutton and Lueth, 1932; Cowdry, 1933; Oille, 1933, etc.). (See Hall, 1936.)

In a similar manner the pathological changes which occur in the coronary arteries and the subsequent changes in myocardium have been studied by many investigators, and the pathological sequence of events is well recognized. Likewise, from the work of Gross (1921), Spalteholz (1924) and Ehrlich, de la Chapelle and Cohn (1931), etc., the distribution and anastomoses of the coronary arteries in man have been accurately described. That the anastomosis between the right and left coronary arteries increases with advancing age has been demonstrated by Gross, Epstein and Kugel (1934). They further showed that this ever increasing anastomosis is further increased by any gradual narrowing of the lumen. Thus the heart, in the sixth and seventh decades, is comparatively well able to survive a progressive occlusion of one or more branches of a coronary artery.

After being able to diagnose the disease and treat the patient clinically, and at the same time appreciate the pathological changes involved, the most important phase at the present time is to understand the nature and the cause of the disease.

A great deal of information concerning "heart disease" has been obtained from experimental occlusion of various branches of the coronary arteries. Experiments of this nature have been carried out almost continuously from the time of Erichsen (1844) and Panum (1862). Cohnheim was the first to make a complete investigation of this phase of cardiac physiology and in 1881 published a comprehensive report on the effects of coronary artery occlusion. Since that time many hundreds of papers have contributed further to our knowledge of the sequelae of coronary occlusion. All of these effects of occlusion are due to a reduction of the blood supply to the myocardium. It is obvious, then, that one must attempt to investigate the factors which would tend to produce either acute or chronic narrowing of the lumen of the coronary vessels, local or general, and the subsequent ischemia of the heart muscles.

Studies on the effects of anoxemia on heart muscle have been reported. Wertheimer (1930) showed that the perfused beating heart maintained its glycogen content so long as sufficient oxygen was supplied. Long and Evans (1932) then proved that anoxemia resulted in a very rapid depletion of the heart glycogen. Himwick, Koskoff and Nahum (1928), Veischer and Mulder (1930) and McGinty (1931) have, in turn, shown that lactic acid and glucose are removed from the blood by the normal heart and converted into glycogen. Himwick, Goldfarb and Nahum (1934) have shown that following coronary occlusion, the infarcted area loses fairly large quantities of glycogen which produce, in turn, an increase in lactic acid and soluble carbohydrates. The infarcted area, which showed a lowered glycogen concentration, contained an average of 260 mg. per cent less than the normal areas.

The lactic acid content of tissues remains low and the glycogen high when the oxygen supply is adequate, but when the oxygen tension is decreased, or in the absence of oxygen, the glycogen decreases and the lactic acid increases. The contractile power of skeletal muscle is lost when the lactic acid increases to 300 mg. per cent, whereas in cardiac muscle, being much more sensitive, fatigue and loss of contractility result when the concentration increases to 70 mg. per cent (Katz and Long, 1925 to 1926). Thus acute anoxemia of the myocardium results in a local increase of lactic acid at the expense of the glycogen, an increase which in some cases exceeds the level where the contraction response could occur (Grayzel, etc., 1934, and Himwick, etc., 1934).

Lewis, Pickering and Rothschild (1930) have shown that a decrease of the blood supply to skeletal muscle, which gave rise to an increased concentration of lactic acid, produced subjective symptoms of pain. The suggestion has been made (Himwick, 1934) that the accumulation of metabolites in the infarcted area of myocardium following coronary occlusion might be the cause of the subjective pain as experienced by patients in angina or during coronary occlusion.

In order to appreciate fully the factors which might influence the degree of ischemia, it is necessary to consider the physiological regulations of coronary blood flow, the effect of altered rhythms and rates, the influence of chemical factors and the effect of metabolites on the oxygen utilization by heart muscle. These physiological considerations have been reviewed by the author (1936).

Assuming that the innervation of the heart and its blood vessels is normal and that other non-local influences are not affecting the mechanics of the heart, we may assume that the normal functioning of the heart depends upon the integrity of its own blood vessels. This in turn depends upon the ability of the coronary arteries to respond to normal physiological stimuli by a change in tone of the vessel wall, whether this be dilatation or constriction. The inability of the coronary vessels to respond normally to efferent stimuli limits the functional capacity of the heart itself and relative degrees of ischemia may result. There are, of course, certain conditions which decrease the blood supply to the heart muscle in the presence of normal coronary arteries. These, as White (1934) points out, are "severe anemia, marked aortic regurgitation, extreme bradycardia, extreme tachycardia, marked temporary hypertension, and blocking of the mouths of the coronary arteries by large vegetations on the aortic valve or by syphilitic aortitis." Otherwise a reduction in the blood supply is usually the result of obstruction or narrowing of the coronary arteries. Narrowing is most commonly the result of atheromatous changes in the vessel wall with subsequent diminution in the size of the lumen. The obstruction may be the result of thrombosis, due to the deposition of platelets, fibrin and cells upon a damaged intima or upon an atheromatous plaque. Sudden occlusion may be the result of thrombi or even plaques breaking

loose from the wall of a larger sized coronary artery and causing occlusion of an artery distal to the initial lesion. Other pathological considerations have been reviewed by the author (1936).

We know then that the clinical entity of "coronary disease" and the pathological changes in myocardium are due to a diminution of the blood supply to the heart muscle and that such diminution is the result of narrowing or obstruction of the coronary arteries by degenerative changes in the vessel walls. Let us consider, then, the factors which are responsible for the degenerative lesions in the coronary arteries.

Many theories have been advanced as to the cause of, or the nature of development of atheroma of the coronary arteries and of arteriosclerosis in general. The inflammatory origin and the suggestion that the changes in the coronary arteries as seen in acute infections are the precursors of arteriosclerosis have to be carefully considered. However, this conception must be only a small factor in the ultimate serious manifestations of coronary disease. On the other hand, certain types of arterial lesions can be produced in rabbits by high protein feeding (Newburgh and Clarkson, 1922, 1923). Hypersuprarenalemia has also been shown (Danisch, 1928) to be an important factor in the cause and development of arteriosclerotic changes. Experimental adrenalin sclerosis has been recorded many times (Thorel, 1915; Cowdry, 1933). Excessive feeding of cholesterol and cholesterol-like substances also has been found to produce arterial lesions in rabbits. This subject has been extended and reviewed by Duff (1935). Joslin (1927) and others have suggested that the high incidence of arteriosclerosis in diabetic patients may be due to an "incomplete oxidation of fats." Arterial changes following the administration of excessive amounts of vitamin D have been reported on by Vanderveer (1931), Ham (1934), etc.

Obviously, then, the cause of the arterial degenerations is unknown.

Although diet, climate, race, etc. appear to have little influence on the incidence of coronary disease, it is nevertheless, much more frequent in males than in females (White and Jones, 1928; Parkinson and Bedford, 1928), and it seems that the high-strung, worried, business and professional man is more susceptible to the disease than is the placid, insensitive individual. This fact in itself should suggest a neurophysiological influence.

It was on this basis that the experiments to be reported were carried out.

Under normal conditions we may assume that the sympathetic and parasympathetic divisions of the autonomic nervous system, which are synergistic in function, are in equilibrium. Further, we may assume that any disturbance of the physiological balance of these nerves may eventually result in pathological changes in the dually innervated organs.

Physiological dysfunction of a group of central nuclei may produce a symptom-complex, from an increase in functional activity in the respective divisions of the autonomic nervous system, which may affect the whole nervous system or only a special localized part of it. Exaggerated "tonus" or "status" of either system does not necessarily imply hyperirritability or

physiological dysfunction of the nerve centers involved, but these may be produced by an excess, either relative or absolute, of stimulating substances in the blood.

In the intact animal the effects of vagus or parasympathetic stimulation are produced through the medium of liberated or synthesized acetylcholine. The parasympathetic nerves are therefore spoken of as cholinergic. In a similar manner the effects of sympathetic nerve stimulation are produced through the medium of a liberated adrenalin-like substance and these postganglionic sympathetic nerves are therefore spoken of as adrenergic nerves. This is true only of the postganglionic sympathetic fibers, since an impulse passing along a preganglionic sympathetic fiber liberates acetylcholine at the synapse in the sympathetic ganglia before the impulse is transmitted through the ganglia to the adrenergic postganglionic fibers. With parasympathetic fibers both pre- and post-ganglionic fibers are cholinergic.

Thus we find that acetylcholine is being liberated constantly in the body producing its effects on all dually innervated organs.

The effect of acetylcholine, whether produced by vagus stimulation or by intravenous injection of the autacoid, is evanescent, due to the very rapid hydrolysis of the acetylcholine by a more or less specific choline-esterase (Stedman, etc., 1933) which is present in the circulating blood and other tissues of the body. In general, too, the effects of parasympathetic excitation are inhibited by atropine and enhanced by eserine, the eserine being effective through its inhibition of the choline-esterase. Thus the regulation of the whole parasympathetic division of the autonomic nervous system depends upon the integrity of the acetylcholine-esterase mechanism (Hall and Ettinger, 1937; Hall and Lucas, 1937).

It seemed reasonable, therefore, that a functional imbalance of the two divisions of the autonomic nervous system might result from long-continued daily intravenous injections of this vagomimetic substance, acetylcholine, a substance which occurs naturally and continuously in the body.

## EXPERIMENTAL

Acetylcholine solution, 1:10,000, was injected intravenously into unanesthetized dogs. Sterile technic was used. The daily injection period was 90 minutes, during which time the animal received 50 mg. of acetylcholine (approximately 4 mg. per kilo. body weight) in 500 c.c. of isotonic saline. Daily injections, seven days a week, were continued until the death of the animal.

In the hope of correlating any clinical symptoms with the experimental results, routine laboratory procedures were carried out on each dog each week (Hall, Ettinger and Banting, 1936). Fatal coronary artery and myocardial damage was produced in these dogs after receiving 25 to 226 (in two dogs over 400) continuous daily injections of acetylcholine; two young dogs receiving similar injections died from gastrointestinal disturbances

(Banting and Hall, 1937). In the older dogs the arterial damage was more marked than in the younger dogs, although in all cases clinical evidence of progressive myocardial failure with subsequent death was noted. Such evidence included attacks characterized by restlessness and distress, leukocytosis, elevated temperature, dyspnea, decreased blood pressure and changing electrocardiograms.

One of the earliest changes observed in the electrocardiogram was a prolongation of the PR interval even up to 0.4 second. Frequently the QRS interval was irregularly increased usually in association with ventricular extrasystoles. The extrasystoles often appeared in bouts of four or five (figure 1a) but more frequently appeared singly. The point of origin of these ectopic beats could not be determined from the electrocardiogram.

After an "attack" the electrocardiogram usually showed an irregularity in voltage of the R-wave with the tendency for a deeply negative T to be associated with an increased voltage of the corresponding R. In these instances the QRS interval was prolonged. Quite frequently complete and partial heart block was evident, there often being as many as six or eight missed beats, to be followed almost invariably by a 2:1 block with abnormal T-waves (figure 1b). Often following an "attack" the T-waves became completely inverted (figure 1c). The variable shape and voltage of the T-waves, at the same time considering the degree of myocardial failure exhibited by these animals, suggests a decrease in blood supply to heart muscle with resulting cardiac infarction. The great regularity with which auricular fibrillation was recorded in these animals (figure 1d) again suggests a grade of heart disease. Auricular ectopic beats were infrequently noted.

Examination of routine sections of the heart showed areas of early hyaline degeneration of myocardium (figure 2), recent infarcts of myocardium, including papillary muscles (figure 3), hyaline degeneration of the media of the medium and smaller sized arteries, thrombosis of branches of coronary artery, recanalization of occluding thrombi (figure 4), fatty degeneration of myocardium in the region of infarction and areas of fibrosis (figure 5).

It is interesting to note here that almost all the younger animals under the influence of exaggerated parasympathetic tone exhibited melena and hematemesis and at autopsy showed congestion of the mucosa in the stomach and duodenum, and in several cases ulceration had occurred. Inhibition of parasympathetic overactivity by atropine prevented the occurrence of such lesions. Eserine, on the other hand, enhanced the acetylcholine and vagal effects (Manning, Hall and Banting, 1937).

Control experiments have been carried out and reported by Hall, Ettinger and Banting, 1936; Banting and Hall, 1937; Manning, Hall and Banting, 1937, etc., and no abnormal clinical pathological manifestations were observed.

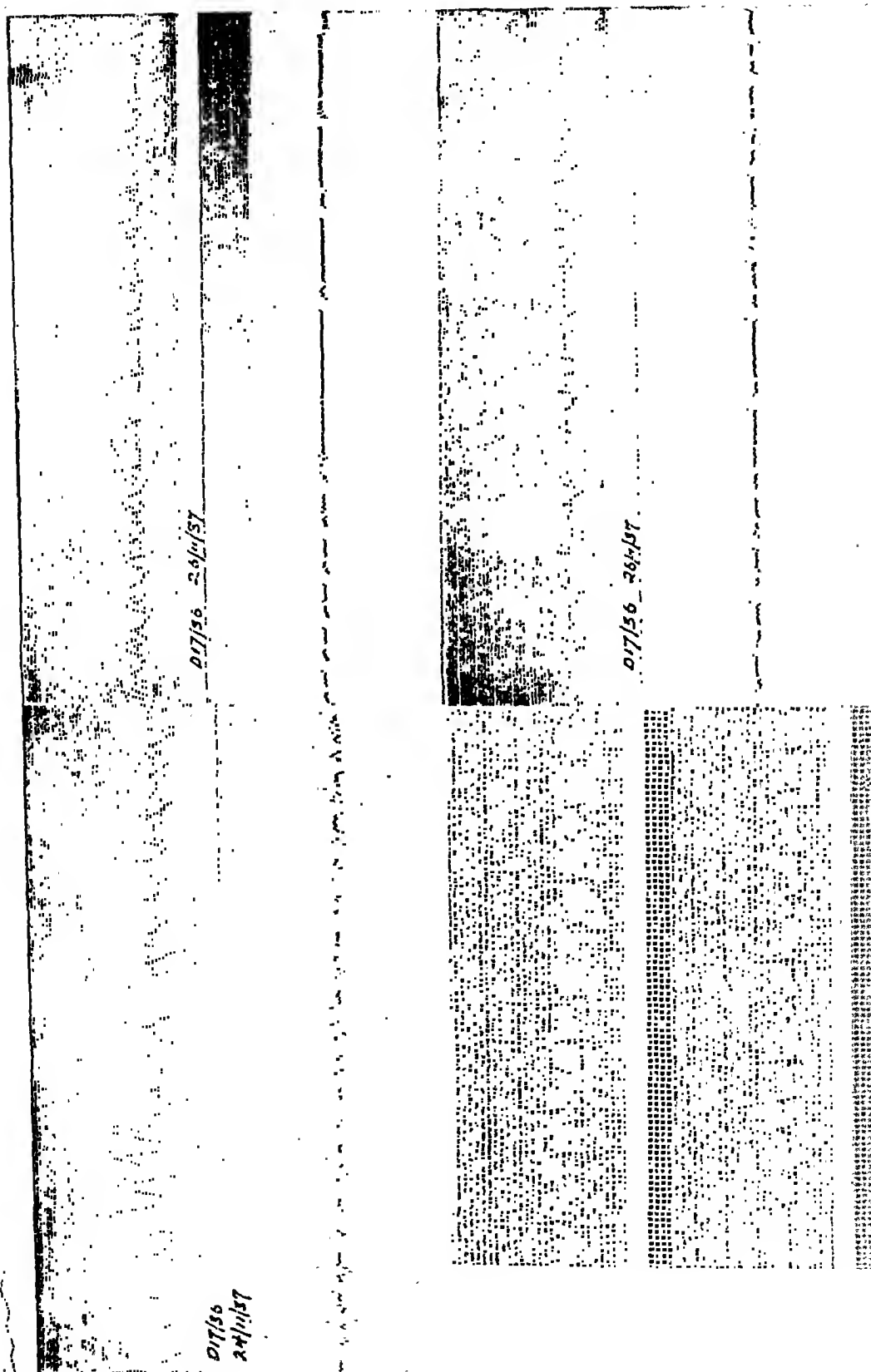


FIG. 1. Electrocardiographic changes induced in dogs by repeated injections of acetylcholine. (a) (Upper left) Extrasystoles; (b) (Upper right) Heart block; (c) (Lower left) Inversion of T-wave; (d) (Lower right) Auricular fibrillation. Ectopic foci, ventricular.

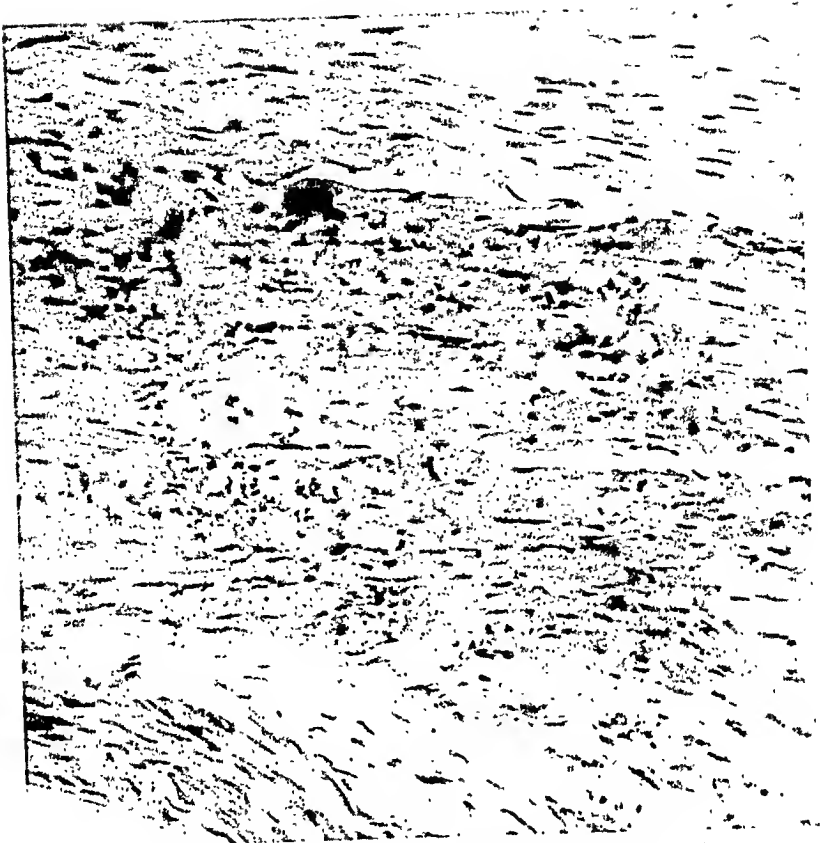


FIG. 2. Early hyaline degeneration of the myocardium.

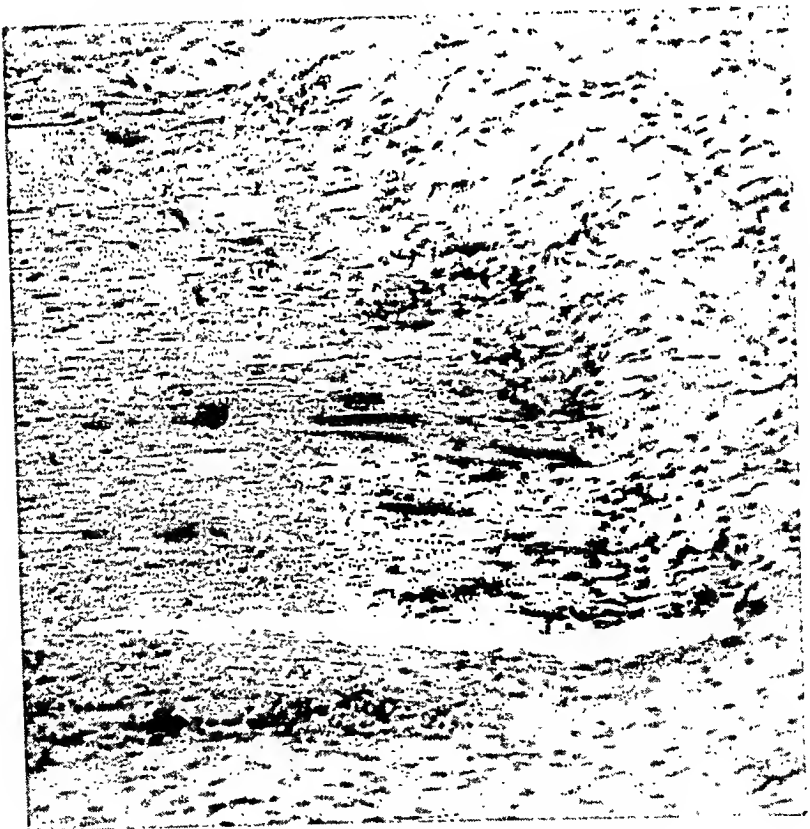


FIG. 3. Recent infarct of the myocardium.

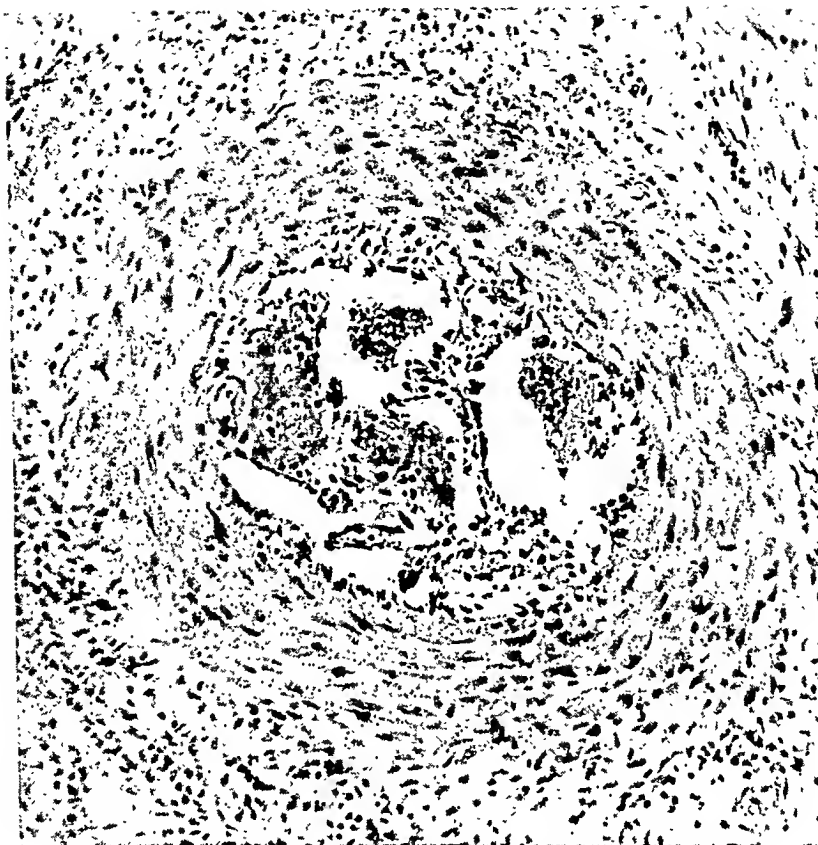


FIG. 4. Thrombosis of coronary artery with recanalization.

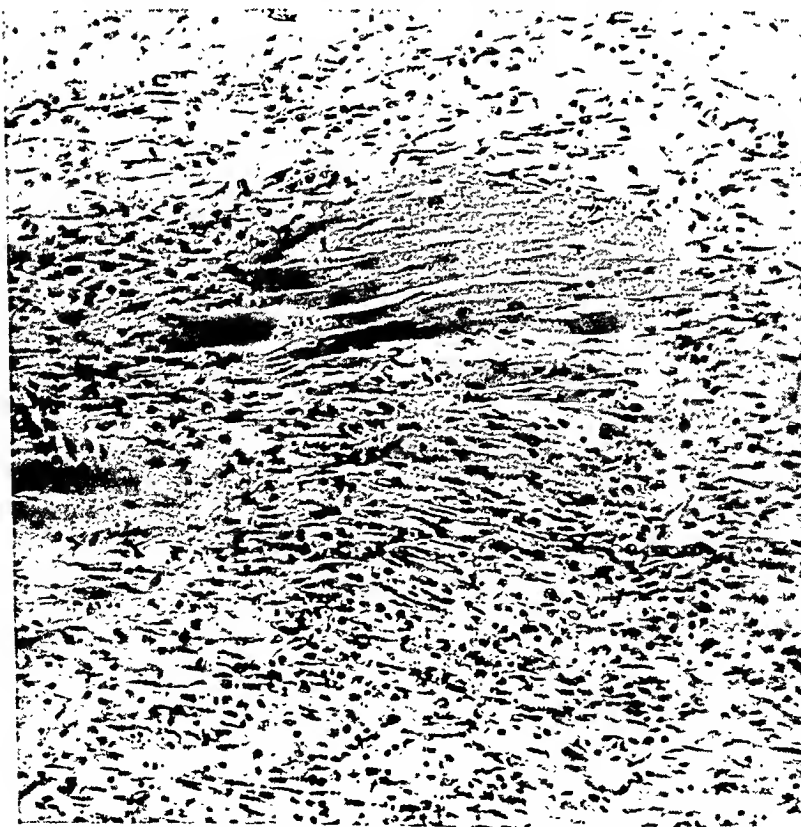


FIG. 5. Area of fibrosis in old infarct.



In order to show the similarity between the pathological changes in the myocardium of these dogs with those produced by actual ligation of the coronary arteries, Hall and Manning (1938) ligated the left anterior descending branch of the coronary artery at the same point in eight litter-mate puppies. The pups were sacrificed 6 hours, 12 hours, 24 hours, 48 hours, 3 days, 7 days, 14 days and 21 days after occlusion. In another series the left circumflex branch was ligated in six litter-mate pups. These were sacrificed 12 hours, 24 hours, 48 hours, 3 days, 7 days and 14 days after occlusion. The right coronary artery was similarly ligated in another series of litter-mate pups.

The earliest change observed in heart sections from these animals was a diffuse hyaline degeneration—the nuclei still staining well. In the next 24 hours the infarcted area became more well defined—the ischemic muscle fibers staining poorly and showing loss of striations. In the 48 hour sections fibrous tissue cells are seen and within 72 hours the fibrosis is well developed. Sections taken 7, 14 and 21 days after ligation show the progressive development of the fibrosis with the formation of macroscopic scars.

The similarity between the myocardial changes as observed in the dogs dying of "coronary disease" and in those killed after varying periods of acute coronary occlusion is striking.

In the original hypothesis it was intimated that the effects of physiological dysfunction might be evidenced by pathological changes in one or more local areas. This has been demonstrated experimentally by producing an autonomic imbalance by the exaggeration of parasympathetic effects.

Secondly, then, the effects of producing essentially the same type of autonomic imbalance by a relative decrease in sympathetic tone will be considered.

It has been recorded by Banting and Gairns (1926) and others, that duodenal and gastric ulcerations with hematemesis, melena, etc. commonly occur in adrenalectomized dogs. In view of the sympathetic failure in adrenal insufficiency, described first by Elliott (1914) and more recently by Cleghorn (1937, 1938), this might be considered a parasympathetic effect, resembling as it does so closely the lesions observed by Hall, Ettinger and Banting (1936). If this were so it might be expected that cardiac changes as found by these authors, might be met in animals dying of adrenal insufficiency. No reference has been found, however, describing the occurrence or even intimating the possibility of cardiac lesions and few referring to cardiac dysfunction in experimental adrenal insufficiency.

The close examination of the hearts of animals dying of adrenal insufficiency, however, revealed cardiac lesions. This finding, which apparently had not been previously described, was reported in brief by Banting and Hall (1937) and by Hall and Cleghorn (1937), who showed electrocardio-

graphic and kymographic evidence of marked cardiac dysfunction as a result of suppression of sympathetic effects.

More recently Hall and Cleghorn (1938) have reported more fully on this subject. The animals (dogs) used were bilaterally adrenalectomized in two stages. Post-operative treatment included intravenous normal saline and cortical extract, followed by subcutaneous injections of the hormone twice daily until the animal was gaining weight and was otherwise in good health. At this time a series of normal electrocardiograms was taken and chemical estimations of blood were made. The administration of cortical extract was then discontinued. During the period of insufficiency routine examinations of blood were made; electrocardiograms were taken with increasing frequency as the clinical condition of the animals became progressively more grave.

Periodically throughout the stage of insufficiency evidence of dyspnea and distress was noted. Frequently, too, coarse râles were heard following such an attack. This pulmonary edema was usually evident at autopsy.

Extrasystoles, cardiac irregularity, changing T-waves, extreme bradycardia followed by a marked pulse deficit and at times associated with the complete absence of P-waves indicated a definite cardiac dysfunction. The failure of the heart of these animals to accelerate following atropine indicated the inability of the sympathetic mechanism to assume control when vagal influences were suppressed.

In histological sections taken from the hearts of these animals arterial and myocardial damage was seen. In some sections recent thrombus formation was observed with its attachment to vessel wall at the site of a break in the continuity of the endothelial lining. Other sections showed arteries whose walls were markedly edematous and in some cases arterial spasm was evident. (Figure 6.) Complete thrombosis of a number of medium-sized coronary arteries was also noted and in a few instances (figure 7) organization and recanalization of the thrombus had taken place. In two cases degeneration of the media of larger-sized coronary arteries was observed. Early hyaline degenerative changes were seen in sections of myocardium.

Macroscopic ulcers were frequently found in the duodenum and prepyloric region of the stomach.

Essentially the same kind of experiments has been reported by Bodansky and Brindley (1937) in confirming our work, in which they produced myocardial degeneration and endothelial proliferation of the coronary vessels in rats following 85 to 90 daily subcutaneous injections of acetylcholine.

Hall (1938) again showed that myocardial and coronary artery changes were produced by the daily injection of acetylcholine in rats and rabbits. Of greatest interest was the preponderance of peripheral arterial lesions in rats following the daily injection of acetylcholine for periods up to 400 days. The process consists, in the aorta, of an intimal thickening with a prolifera-

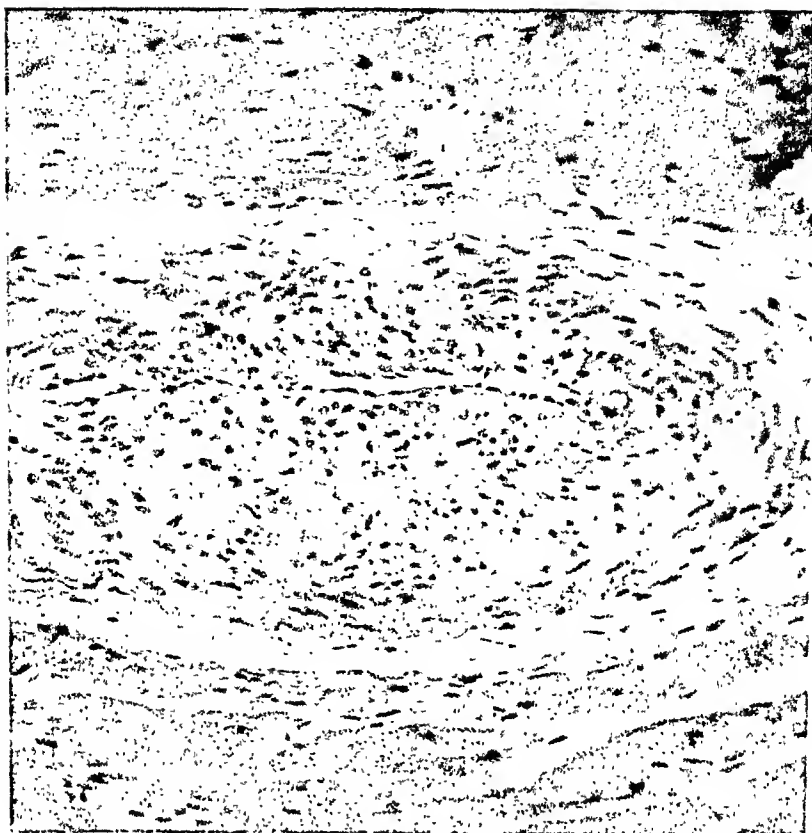


FIG. 6. Spasm of coronary artery—with thickening. Adrenalectomized dog.

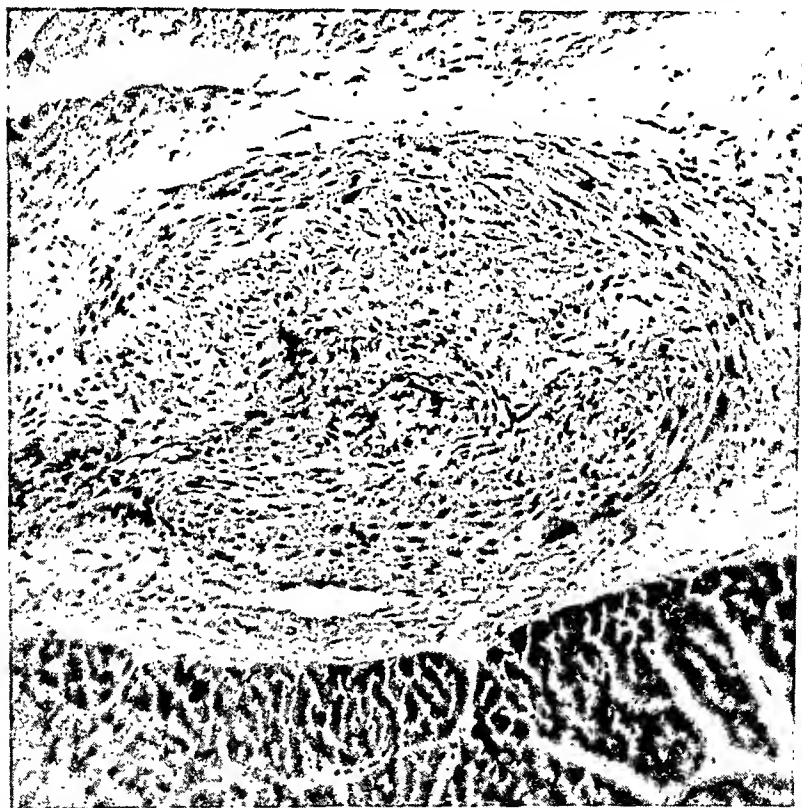


FIG. 7. Complete occlusion of the coronary artery with some organization. Adrenalectomized dog.



FIG. 8. Intimal thickening of aorta due to endothelial proliferation. (Rat)



FIG. 9. Areas of fatty degeneration and calcification. Splenic artery of rat.

tion of the endothelial cells (figure 8). In the thickened area fine fibrils were seen producing a thickened subendothelial layer. The internal elastic lamina was, in several instances, frayed and split.

A medial degeneration with calcareous deposits was observed, associated with intimal changes, in some of the smaller arteries (figures 9 and 10). In many cases thrombosis had taken place in the atheromatous vessel (figure 10). In mesenteric vessels there was a very marked perivascular response—resembling quite closely periarteritis nodosa.



FIG. 10. Atheromatous plaque. Artery of rat.

Thus it is seen that in different species different arterial changes are produced by the same physiological mechanism. In the dog the lesions are chiefly medial, while in the rat intimal changes, with or without associated medial damage, are the prominent features. This is the case, of course, in the human type of arteriosclerosis.

The interpretation of progressive electrocardiographic records, the analysis of acute experimentation and the study of the microscopic sections of the animals used in these different experiments supply evidence to show the importance of a normal functional equilibrium between the two divisions of the autonomic nervous system.

## SUMMARY

1. Myocardial and coronary artery damage have been produced in dogs following chronic over-activity of the parasympathetic nervous system.
2. Gastric and duodenal congestion and ulceration have been produced by the same mechanism.
3. Similar lesions in the heart and in the gastrointestinal tract have been described in dogs dying of adrenal insufficiency.
4. Myocardial degeneration, atherosclerosis of the aorta and other vessels with or without associated arteriosclerosis have been produced in rats following chronic injections of the vagus substance—acetylcholine.

# PNEUMOCOCCIC LOBAR PNEUMONIA: A REPORT OF 245 CASES WITH SPECIAL REFERENCE TO SPECIFIC SERUM THERAPY \*

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It is our object in this report to present data accumulated between January 1935 and July 1937, in the treatment of lobar pneumonia, particularly with reference to specific serum therapy.

It has been our aim to examine carefully the results in the use of specific serum in suitable cases and to compare these results with those obtained in other cases in which, for some reason, serum was not used. We realize that the number of our cases is small compared to figures from larger institutions, but we wish to make our own modest contribution to indicate what good results can be obtained even in a hospital of moderate size. This hospital has four hundred beds and is one of two which serve a city with a population of about 150,000. Between January 1935 and July 1937, there were 3740 medical admissions, of which 245 cases were diagnosed lobar pneumonia—an incidence of 6.5 per cent.

In the past few years many contributions have been made to the study of lobar pneumonia and the use of specific serum treatment. We are deeply indebted to Cole <sup>1</sup> and his co-workers of Rockefeller Institute, to Cecil and Plummer <sup>2</sup> of Bellevue Hospital, to Sutliff and Finland <sup>3</sup> at the Thorndike Memorial Hospital and to others for their researches in this field. Although these workers have emphasized the successful results obtained with specific serum in pneumonias specifically typed, it appears that many medical men still hesitate to adopt this form of therapy in a disease which, even under the most favorable circumstances, must be regarded seriously.

According to the statistics <sup>4</sup> of the Metropolitan Life Insurance Company, pneumonia is still the third greatest cause of death. According to Cecil, <sup>5</sup> the combined average mortality of the pneumonias is close to 25 per cent. A short time ago, Benjamin <sup>6</sup> and his co-workers at the Cincinnati General Hospital pointed out several reasons why medical men are relatively slow in adopting serum therapy. They referred to the technical difficulties in sputum typing and commented on the fact that many practitioners still entertain some doubts of the efficacy of this treatment.

Cecil <sup>7</sup> and others in their reports stated that within the last decade, the curative value of specific serum has been definitely established in Types I and II, and that evidence is being accumulated to show that specific serum is also efficacious in Types V, VII, VIII and XIV. They, too, deplored the fact that the use of specific serum has not become more general, and mentioned as reasons the lack of facilities for typing pneumococci, the high

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From the Laboratory of the Bridgeport Hospital.

cost of the serum and hesitancy of the general practitioner to use it intravenously.

Gradually in the past few years, more and more laboratories have developed facilities for typing sputum. New York and Massachusetts have long since equipped their central and branch laboratories. Connecticut keeps its physicians advised of such laboratories available for their use. The high cost of serum still remains an important factor in preventing the general adoption of this procedure and the problem of distributing this burden must still be worked out. As to doubts in the minds of physicians of the efficacy of the treatment and their hesitancy in adopting it—these factors can only be obviated by familiarity with the statistics emanating from the great medical centers. These skeptical medical men will be won over only as more and more experience is accumulated and reported in the literature. More recent reports have unanimously indicated that the most valuable and at times the one life-saving procedure is the early use of adequate, specific serum in the treatment of lobar pneumonia.

It must be realized that our progress in the therapy of pneumonia is almost entirely due to reports coming from medical centers and large city hospitals. At these institutions the number of cases, the facilities for research and for compiling statistics are far greater than at smaller hospitals. The analysis, which we have made from our results, has been necessarily restricted due to the small number of cases and limited technical assistance. It is all the more interesting to note that with our limitations we have obtained such highly satisfactory results. This should be a stimulus to other institutions of similar size to consider specific serum therapy in all suitable cases.

First, let us define the condition for which we recommend it. We consider lobar pneumonia as an acute inflammation, involving one or more lobes of the lung, produced by some strain of pneumococcus. Since the prognosis and the treatment depend so much on the specificity of the bacterial agent, we have placed particular stress not only on identifying the inciting organism but also on the technic of typing-out the specific strain of pneumococcus. Great progress has been made since Neufeld and Händel in 1909 working in Germany and Dochez and Gillespie in the United States in 1913 showed that all pneumococci were not alike and that the different types could be identified and differentiated. Gradually more and more strains of pneumococci have been separated serologically so that now there are 32 distinct types. Due to the limited size of our laboratory staff and to the fact that up to the time this paper was written there were available but a few specific sera for therapy, we in the laboratory have typed out only the following strains: Types I, II, III, IV, V, VI, VII, VIII and XIV. Other pneumococci were identified and reported only as belonging in certain polyvalent mixtures which corresponded to those found in the commercial diagnostic sera sets. We are planning to go further and type out specifi-



cally each of the 32 types of pneumococci as the commercial specific sera become available for each.

The basis of this study is 245 cases of lobar pneumonia caused by pneumococci. Our criteria in making the diagnosis of pneumococcus lobar pneumonia were: Sudden onset, a chill and fever, pain in the chest and cough with rusty sputum which, on typing, showed pneumococci. In each case the above findings were corroborated by physical examination showing lobar consolidation. In the presence of doubtful physical findings, roentgen-ray examination showed consolidation. Of the 245 cases there were 166 adults and 79 children. Table 1 shows the incidence of males and females, of adults and children, and the mortality as found in our entire series.

It is seen that the incidence among males was slightly less than twice as high as among females but the mortality among the males was 2.5 times that of females. The mortality in the adult group was 14.4 per cent. Painton<sup>8</sup> found an incidence of males to females in the ratio of 3 to 1 with 10 per cent higher mortality among the males. The greater incidence among

TABLE I  
Incidence and Mortality According to Sex

	No. Cases	% Incidence	No. Deaths	% Mortality	% Mortality
Adults					
Male.....	109	44.5	17	15.7	} 14.4
Female.....	57	23.2	7	12.3	
Children under 12 years					
Male.....	48	19.6	0	0	} 1.2
Female.....	31	12.7	1	3.2	
Total.....	245		25	10.2	

males is probably due to their occupations, living conditions and habits, including the greater use of alcohol.

Table 2 shows the incidence of pneumonia cases as distributed among the age groups and sexes as indicated. There were 79 children under the age of 11 years in our series—an incidence of 32.2 per cent with only one death or 1.2 per cent mortality. This was a female, four years of age, seen for the first time on the eleventh day of her illness, having an unclassified type of pneumococcus pneumonia with empyema. She died three days after admission and postmortem findings confirmed the diagnosis. When we consider the entire series it is apparent that 80 per cent of all pneumonia cases seen at this hospital were in persons under the age of 50 years. It is well known that age is an important factor in the mortality. Between the ages of 41 and 60, the mortality rate was 18.5 per cent, while beyond 60 the mortality rose to 46 per cent. The single decade showing the highest incidence among adults was between 41 and 50 years, while the single decade showing the highest mortality was between 71 and 80 years.

As a matter of interest, we have compared the relative incidence of individual and multi-lobar involvement on the right and left sides. Right sided involvement was 1.5 times more frequent than the left sided involvement, as seen in table 3. The mortality in right lung involvement was 2.5 times as high as when the left lung was involved.

TABLE II  
Incidence and Mortality among Age Groups

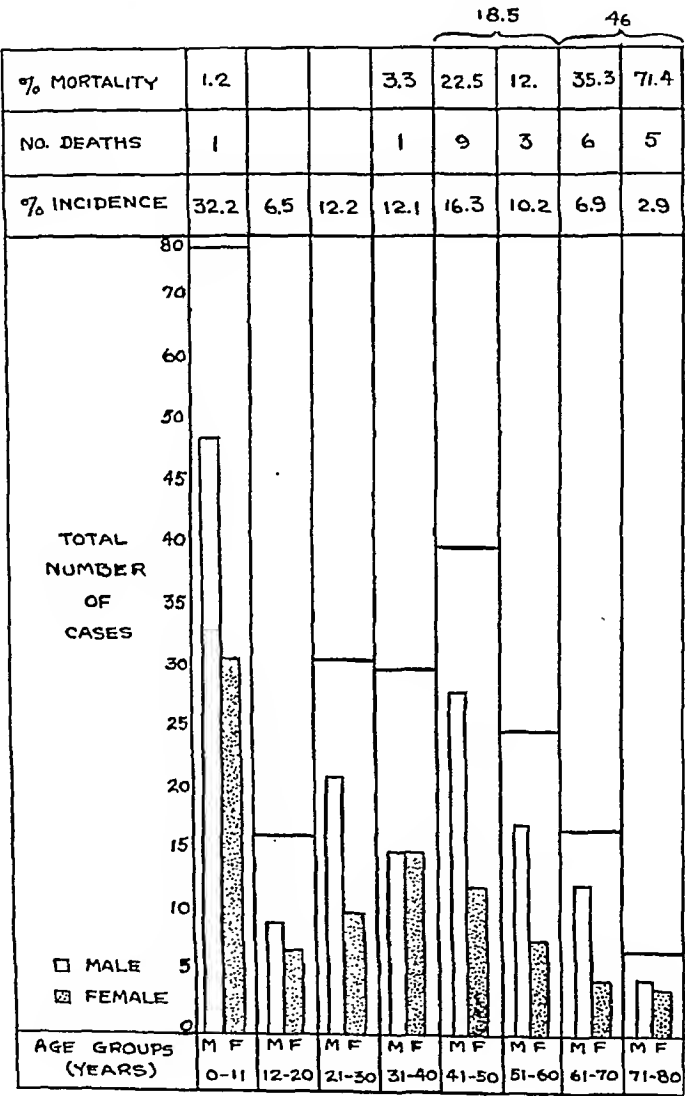


TABLE III  
Incidence of Lobe Involvement

Lobe	No. Cases	% Incidence	No. Deaths	% Mortality
R. U. L.....	37	15.1	4	72
R. M. L.....	24	9.8		
R. L. L.....	96	39.0	14	
L. U. L.....	11	4.	1	28
L. L. L.....	100	40.8	6	

Table 4 shows the incidence and mortality of the pneumonias according to the serological types. It is noted that Type I pneumonia occurred in 104 or 42.5 per cent of all the cases studied.

Typical lobar pneumonia cases, in which the inciting organism was not serologically identified as to type because of our limited facilities, numbered 54 or 22 per cent of the total. Up to the time of writing, there are no available sera for members of this unclassified group. In this table we note that the mortality in the Type I pneumonias, for the combined serum-treated and non-serum-treated cases, is 4.8 per cent; compared to the crude mortality for the entire series, which is 10.2 per cent. It has been shown by many extensive reports that specific serum reduced the mortality in Type I pneumonia. As more evidence is accumulated in the specific treatment of the other types for which there is available serum, we feel that there will be an appreciable reduction in the morbidity and mortality in those types as well.

In the review of this series of cases we found no standard or routine

TABLE IV  
Incidence and Mortality among Serological Types

Type	No. Cases	% Incidence Cases	No. Deaths	% Mortality
I	104	42.5	5	4.8
II	3	1.2	0	
III	10	4.1	3	30.
IV	13	5.3	2	15.
V	14	5.7	2	14.3
VI	4	1.6	0	
VII	15	6.1	0	
VIII	22	9.0	2	9.1
XIV	6	2.4	0	
Unclassified	54	22.0	11	20.4
Total	245		25	10.2

dosage of serum, since the cases were selected from the services of several physicians and the series included both general and private cases. However, it was noted that 54 cases of Type I pneumonia, or 64.3 per cent, were given doses varying between 40,000 and 100,000 units. The writer has adopted the plan of giving the patient an initial dose of 100,000 units of serum as soon as careful skin and eye tests were found negative. If the temperature did not fall in four hours, another 60,000 units was given. We feel that large doses of serum given at the earliest moment after careful typing and serum-sensitivity tests have been completed, will produce the best results.

In table 5 there is presented the serum-treated and non-serum-treated cases according to the various types of pneumococci found.

There were 120 cases treated with specific serum with four deaths—a mortality of 3.3 per cent. In the non-serum-treated cases, which numbered 125, there were 21 deaths or 16.8 per cent mortality. The unclassified

TABLE V

Comparison of Mortality between Serum- and Non-Serum-Treated Cases

Pneumococcus Type	Total No.	Serum Cases			Non-Serum Cases		
		No.	Deaths	% Mor-tality	No.	Deaths	% Mor-tality
I	104	84	3	3.6	20	2	10.
II	3	3					
III	10				10	3	30.
IV	13				13	2	15.
V	14	8	1	12.5	6	1	16.6
VI	4				4		
VII	15	11			4		
VIII	22	11			11	2	18.2
XIV	6	3			3		
Unclassified	54				54	11	20.4
Total	254	120	4	3.3	125	21	16.8

type of pneumonias showed 11 deaths or a mortality of 20.4 per cent. Of the 104 Type I pneumonias, 84 cases or 80.8 per cent were given specific serum. There were three deaths in this group—a mortality of 3.6 per cent. Two of these three patients who died, came into the hospital on the third and seventh days of their illnesses, respectively, both were alcoholics in delirium tremens and both died within 24 hours. The third patient was a woman seen on the seventh day, who died within 24 hours after admission. In the Type I non-serum-treated group, there were 20 cases with two deaths or a mortality of 10 per cent. One of these patients was a male, seen on the third day with a positive blood culture who, for some reason, did not receive any serum. He died within 24 hours. The other patient was a female, age 75 years, a chronic alcoholic, who died within 24 hours and post mortem showed consolidation of the left lower lobe and right middle and lower lobes with empyema and pericarditis. Grouping all the Type I patients, the five deaths gave a mortality rate of 4.8 per cent but all five were in extremis when admitted and died within 24 hours.

When we compare the mortality of 16.8 per cent in the non-serum-treated cases with the mortality of 3.3 per cent in the serum-treated cases and 3.6 per cent in the serum-treated Type I cases, we note that the reduction in the mortality is most striking. In addition, when Type I cases were treated with serum, there was noted a marked reduction in the morbidity of the patients.

Table 6 shows the distribution of the various types according to the day of illness when first seen. Seventy-eight cases of Type I pneumonia, or 75 per cent, were seen in the first four days, when the administration of serum is likely to be most effective. Clinically, these patients showed marked improvement within a few hours after the serum was given. In the

TABLE VI  
Distribution of Various Types According to Day of Illness on Admission to Hospital

Day of Illness Patient Admitted	Type I	II	III	IV	V	VI	VII	VIII	XIV	Un-classified	Total
1	2	1		1			1	2			7
2	41	2	4	3	4	1	3	4	5	9	76
3	25		3	3	2	3	7	6		12	61
4	10			2	2		1	6		8	29
											7 } 173 76 } or 61 } 70.6 29 } %
5	11		3		2		1			13	30
6	3							2		2	7
7	9			3	4		3	1	1	7	28
8	1										1
9	2										2
10				1						1	2
11								1		2	3

majority of cases, the temperature soon began to fall. In 46.4 per cent of the cases the patients had a crisis and the temperature reached normal within 24 hours. In 72.6 per cent of the cases it reached normal within 48 hours. The pulse rate dropped within normal range, respirations became slower and easier and the general condition was greatly improved. Many times the change in the clinical picture from that of a severely ill person to one who sat up in bed within a few hours after receiving serum, seemed miraculous. In the non-serum-treated cases only two had a crisis within 48 hours, the other 16 cases terminating by lysis. In the cases treated with specific serum, other than Type I, there were 17 cases or 54.8 per cent that showed a crisis within 48 hours while in the non-serum-treated cases other than Type I only 2.3 per cent terminated by crisis. Although our series is small, there is no doubt in our minds that the administration of serum precipitates the crisis in about three-fourths of the cases, with a concomitant amelioration of symptoms.

As to the use of specific serum in pneumonia other than Type I, the number of our cases is too small to permit any conclusions. In comparison to the reports of other observers, the incidence of Type II pneumococcus pneumonia in this series was surprisingly small. For some reason only three Type II pneumococcus pneumonias were noted. All of these were given serum and had prompt crisis with recovery.

In Type V cases, which numbered 14, eight were given serum. One patient was seen on the seventh day of his illness. He had a positive blood culture and although given 280,000 units of serum, he died nine days after admission. At post mortem there was found a resolving pneumonic consolidation of the right upper and middle lobes with a purulent mediastinitis. The other fatal Type V case received no serum. He was seen on the seventh day, died three days later and at post mortem showed consolidation of the right upper and lower lobes.

There were 15 Type VII cases, 11 of which received serum and four did not. They all recovered but the clinical course of those receiving serum was much milder and the hospitalization of the serum-treated cases averaged 11.2 days, while in the non-serum-treated cases hospitalization averaged 22 days.

Of the Type VIII cases, there were 22, of which 11 were given serum and 11 were not. In the serum-treated cases, hospitalization averaged 14.7 days, while in the non-serum-treated cases hospitalization averaged 17.4 days. In the latter group, two died—a mortality of 18.2 per cent. Both of these fatal cases were seen on the seventh day, one of them a pregnant woman who aborted during her illness and died five days after admission and at post mortem showed empyema in the right chest.

There were only six cases of Type XIV, three of which were given serum and three were not. All recovered and the entire number of cases is too small to comment upon.

Table 7 shows the incidence of complications. Empyema developed in 17 instances (6.9 per cent). It is interesting to note that nine of these

TABLE VII  
Incidence of Complications

Complication	No. Cases	% Incidence
Empyema.....	17	6.9
Otitis Media.....	5	2.1
Pleural Effusion.....	2	0.8
Pericarditis.....	1	0.4
Mediastinitis.....	1	0.4
Total.....	26	10.6

empyema cases occurred in Type I pneumonias which were given serum and two in Type I which were not given serum. The other six empyema cases were distributed among the other types. Of all the fatal cases, empyema was found in only three—one in a Type I non-serum-treated case and two in the unclassified group.

#### COMMENTS ON SERUM THERAPY

We realize that the total number of serum-treated cases—120 in our series, is small compared to reports from larger institutions. According to the most recent statistics<sup>a</sup> in the *Journal of the American Medical Association*, out of 712 accredited hospitals throughout the United States, there are 582 hospitals having 400 beds or less. Our hospital has only 400 beds but it is apparent that hospitals of this size or smaller form 81.7 per cent of the hospitals in this country. In view of this fact, our results are interesting and instructive.

Since there is no method to determine in advance the minimum effective

dose of serum in any case, we believe that a relatively large dose of 100,000 units should be given at once, after specific typing and serum sensitivity tests have been done. In no case where the cutaneous and ophthalmic tests were negative have we seen any harmful serum reactions, no matter how much serum was given at one dose. This is probably due to the quality of the concentrated and highly purified serum that was used. In all of the 120 serum-treated cases, only 12 cases of serum sickness developed—an incidence of 10 per cent.

Our observations have convinced us that if sufficient serum be given within the first four days, it is possible in the great majority of cases to cut short the course of pneumonia and bring about an earlier recovery than would otherwise take place. Although it is true that the effectiveness of serum is apparently greater the earlier in the disease it is given, our experience indicates that every patient, however late he is seen, should receive it.

In evaluating the effect of specific serum, we consider its effect on the morbidity and mortality. In practically all the favorable cases the temperature fell and symptoms were rapidly ameliorated. The mortality was strikingly lower in the serum-treated cases, being 3.3 per cent, compared to 16.8 per cent in the non-serum-treated cases. These results compare favorably with those reported from the larger institutions.

Although the duration of hospitalization of pneumonia patients varied with the physician and the class of service, it was certain that the hospital stay of those patients treated with serum was much shorter than in the non-serum-treated cases. Without doubt, the greatest reduction in mortality was in the Type I infections. Although our experience with specific serum in the other types was limited, we observed a definite lowering of the mortality in the serum treated cases of the Types V, VII, VIII and XIV. The mortality in this group of serum-treated cases was 3 per cent as compared to 12.5 per cent in the non-serum-treated cases. In our series, 67 per cent of all lobar pneumonias fell into types for which there is available specific serum. This compares with 65 per cent as found by other observers.<sup>6</sup> We feel that none of these patients with types of pneumonia for which there is available specific serum should be deprived of the benefits of this therapy.

The difficulty of providing specific serum because of the high cost is gradually being met by the proper authorities. Increased use, as well as improvement in the methods of manufacture and distribution, have combined to reduce the expense involved. For those who cannot afford to pay the entire cost some other provision must be made, such as state aid, so that even the indigent patient may receive serum when he requires it.

#### SUMMARY AND CONCLUSIONS

1. In a two and one-half year period, 245 cases of lobar pneumonia were studied. Of these 164, or 67 per cent, fell within the Types I, II, V, VII, VIII and XIV, for each of which there is available specific serum.

2. Type I cases numbered 104, of which 84 were treated with serum with a mortality of 3.6 per cent. This was in contrast to the death rate of 10 per cent in untreated Type I cases.

3. In a much smaller number of cases consisting of Types V, VII, VIII and XIV which were treated with specific serum the mortality was 3 per cent compared to 12.5 per cent in the non-serum-treated cases.

4. In a total of 120 serum treated cases, the death rate was 3.3 per cent while in the 125 non-serum-treated cases the mortality was 16.8 per cent.

5. Serum sickness was observed in only 12 cases. Skin and eye tests for sensitivity can reduce serious serum complications to a negligible minimum.

6. From our experience, therefore, Type I serum should be given as early as possible and in large amounts, no matter how late the patient is seen.

7. As for the other specific types for which therapeutic serum is available, our experience indicates that all patients having pneumonia of the types for which therapeutic serum is available, should be given the benefits of specific serum therapy.

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# URINARY DIASTASE IN ACUTE PANCREATIC NECROSIS: AN EXPERIMENTAL INVESTIGATION \*

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UNTIL recently, acute pancreatic necrosis has been considered a surgical emergency and universally regarded as an indication for immediate operation. At present the trend is toward more conservative treatment. Trasoff and Scarf<sup>1</sup> have reviewed this problem and analyzed the records of 16 patients with acute pancreatitis. Three of the four subjected to early operation died, whereas of 12 not operated upon, 9 recovered. Hartlieb<sup>2</sup> is opposed to surgical intervention, and has treated 9 patients expectantly, of whom 7 recovered. Mikkelsen<sup>3</sup> reported 39 examples of acute pancreatitis, all of which were treated conservatively with a mortality of only 7.5 per cent.

If operation is to be deferred as these and other observers advocate, it becomes increasingly important for the physician to be certain that he is dealing with this disease and not with some other abdominal emergency in which delay might be fatal. Various observers (Nordmann,<sup>4</sup> Rost,<sup>5</sup> Foged,<sup>6</sup> McCaughan<sup>7</sup>) indicate that with the aid of laboratory tests for diastase it is possible to establish a preoperative diagnosis of acute hemorrhagic pancreatitis in about 85 per cent of cases. Mushin<sup>8</sup> has reported a gratifying improvement in preoperative diagnostic accuracy since this test has been introduced. When it was not used in doubtful upper abdominal crises the condition was diagnosed prior to operation in only 30 per cent of cases. Following its use, when the urinary diastase has been elevated, operation has confirmed the provisional diagnosis. Equally favorable is the report of Foged,<sup>6</sup> who studied the diastase reaction of the urines of 71 patients with acute pancreatitis. In 70 per cent there was a significant increase in the diastase. Where no test has been employed the preoperative diagnosis is unsatisfactory. Schmeiden and Sebening,<sup>9</sup> in a review of 2,137 cases from various German clinics, found a correct diagnosis in only 21.8 per cent. Colp,<sup>10</sup> in 1930, surveyed 54 cases and of these only 30 per cent were correctly diagnosed before operation. Abell<sup>11</sup> reports a slightly higher percentage, 12 of 30 cases, or 40 per cent.

Diastase was first isolated from the urine by J. Cohnheim in 1863. Its exact origin is not known but most of it appears to be liberated by the pancreatic acini. Extra-pancreatic sources exist, for it is found in the blood after total pancreatectomy. Wohlgemuth,<sup>12</sup> in 1908, introduced a practical quantitative method for its determination and a modification of his original method is the basis of the most commonly employed test today. In principle it is based upon the hydrolysis of starch to maltose, erythro-

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dextrin or achroödextrin by diastase, the result depending upon the concentration of the enzyme, and testing by the addition of iodine. Wohlgemuth's "diastase unit" is the amount of ferment contained in 1 c.c. of urine which at 38° C. and in 30 minutes is able to break down 1 c.c. of 0.1 per cent starch.

In the estimation of diastase in urine, we have used a modification of the Wohlgemuth test. One cubic centimeter of recently voided urine is placed in the first and second of a series of 13 test tubes. To all tubes except the first, 1 c.c. of 1 per cent salt solution is added. The contents of tube two (1 c.c. of urine and 1 c.c. of salt solution) are mixed with a pipet and 1 c.c. of this mixture is placed in the third tube. This procedure is repeated through the series, resulting in dilutions of urine of  $\frac{1}{2}$ ,  $\frac{1}{4}$ ,  $\frac{1}{8}$ ,  $\frac{1}{16}$ ,  $\frac{1}{32}$ , etc., to  $\frac{1}{4096}$ . To each test tube is then added 2 c.c. of 0.1 per cent starch solution. All of the tubes are then placed in a water bath at 38° to 40° C. for 30 minutes. At the end of this time the tubes are cooled to retard hydrolysis and a saturated aqueous solution of iodine is added drop by drop. The iodine causes the appearance of yellow, reddish brown, bluish red or blue in the various tubes. The tube showing the first appearance of the color blue is taken as the end point and the calculation of the diastase value is made from the tube immediately before it. Thus if the fifth tube is the first to show the blue color, the dilution in the fourth tube

2 c.c. (of starch)

is used to determine the diastase units:  $\frac{\text{2 c.c. (of starch)}}{\frac{1}{8} \text{ (dilution of urine)}} = 16$ . By

this method diastase values up to 8192 can be determined.

Many diastase determinations have been made on normal individuals and on patients with various illnesses. Values between 4 and 32 units are considered normal. Foged,<sup>6</sup> who has studied the urine diastase in over 4,000 patients, considers only amounts higher than 300 units definitely pathological. In 59 of the 71 cases of acute pancreatic necrosis which he studied, values of 1200 or more were recorded. Beigler and Marcus,<sup>13</sup> who have employed the Wohlgemuth method, examined 237 patients with various abdominal conditions. In this group there were 15 with acute pancreatic necrosis and in these, diastase values were always between 320 and 2000 units. Rost<sup>5</sup> also has reported uniformly high urine diastase values in this disease. In 10 of his 13 patients, between 1000 and 8000 units were present; and in 2, between 128 and 258 units. In Mushin's<sup>8</sup> series of 26 cases the diastase value ranged between 50 and 4100 units. From the literature it may be concluded that in acute pancreatic necrosis there is a prompt elevation in the diastase values beginning six to eight hours after the onset of the disease. Following this rapid rise there is a return to normal, usually by the end of the third day. Therefore, to be of any value, the urine must be tested during the first three days. Even by the end of 36 hours, the diastase value may have fallen to normal.

Among the other pathological conditions which have been observed to cause an elevation in urine diastase, common-duct stone is the most frequent. Values over 300 were recorded in 61 per cent of a series of 69 patients with common-duct stone studied by Foged.<sup>9</sup> This observer considers an elevated diastase value as the surest of all laboratory procedures when confronted with a differential diagnosis between hepatitis, cancer of the pancreas, and common-duct stone. However, a stone lodged in the common-duct does not necessarily bring about an elevated diastase. Severe acute cholecystitis has been noted on several occasions to give an abnormal reading. All observers stress that this test, as any other laboratory procedure, must be considered only an adjunct to the clinical picture and history. There is agreement that, although increased values may occur in other acute abdominal conditions, a normal finding excludes a pathologic process located in the pancreas.

In the course of an experimental investigation of the pathogenesis of acute pancreatic necrosis, opportunity was afforded to test the validity of the urinary diastase reaction on carefully controlled material. (The tissue lesions produced will be reported elsewhere.)

Acute pancreatic necrosis has been produced in dogs by the injection, under surgical technic, of small droplets of metallic mercury into one of the

TABLE I

Urinary Diastase Determinations Following Experimental Pancreatic Infarction

	Dog No.	Number of Diastase Determinations	Highest Diastase Value	Series Considered Satisfactory	Remarks
Food as Pancreatic Stimulus	VI	22	64 units	Yes	Chronic interstitial pancreatitis.
	VII	19	256 units	Yes	Pancreatic abscess.
	VIII	9	128 units	No	Acute pancreatic necrosis. Perforation of duodenum. Generalized peritonitis. Lived only 22 hours.
	IX	4	16 units	No	Died within 2 hours.
	X	1	8 units	No	Acute pancreatic necrosis. Death 22 hours post-operative. Duodenal perforation.
	XI	2	4 units	No	Died within 2 hours.
	XII	18	1024 units	Yes	Pancreatic abscess.
	XIII	14	256 units	Yes	Acute pancreatic necrosis.
	XIV	17	32 units	Yes	Small abscess of pancreas.
	XV	11	2 units	Yes	Small abscess of pancreas.
	XVI	15	32 units	Yes	Small chronic pancreatic abscess.
Acetyl- $\beta$ -Methyl-Choline Chloride and Physostigmine	XVII	17	256 units	Yes	Pancreatic abscess.
	XVIII	10	1024 units	No	Acute pancreatic necrosis. Perforation of duodenum. Generalized peritonitis. Death 26 hours post-operative.
	XIX	8	128 units	Yes	Acute pancreatic necrosis. Small abscess.
	XX	11	128 units	Yes	Chronic interstitial pancreatitis.
	XXI	13	8192 units	Yes	Subacute hemorrhagic pancreatitis.

pancreatic arteries at a time when the pancreas was stimulated to the height of its secretory activity. Sixteen animals were used, divided into two groups. In one series of 10, food was used as a stimulus by giving a meal of meat and cereal two hours before operation. In a second group of six dogs, subcutaneous injections of acetyl- $\beta$ -methylcholine chloride, in doses of 0.5 mg. per kilo of body weight, together with 1 mg. of physostigmine salicylate, were given. Friedman and Thompson<sup>14</sup> have shown that these drugs given together are powerful stimulants to pancreatic secretory activity.

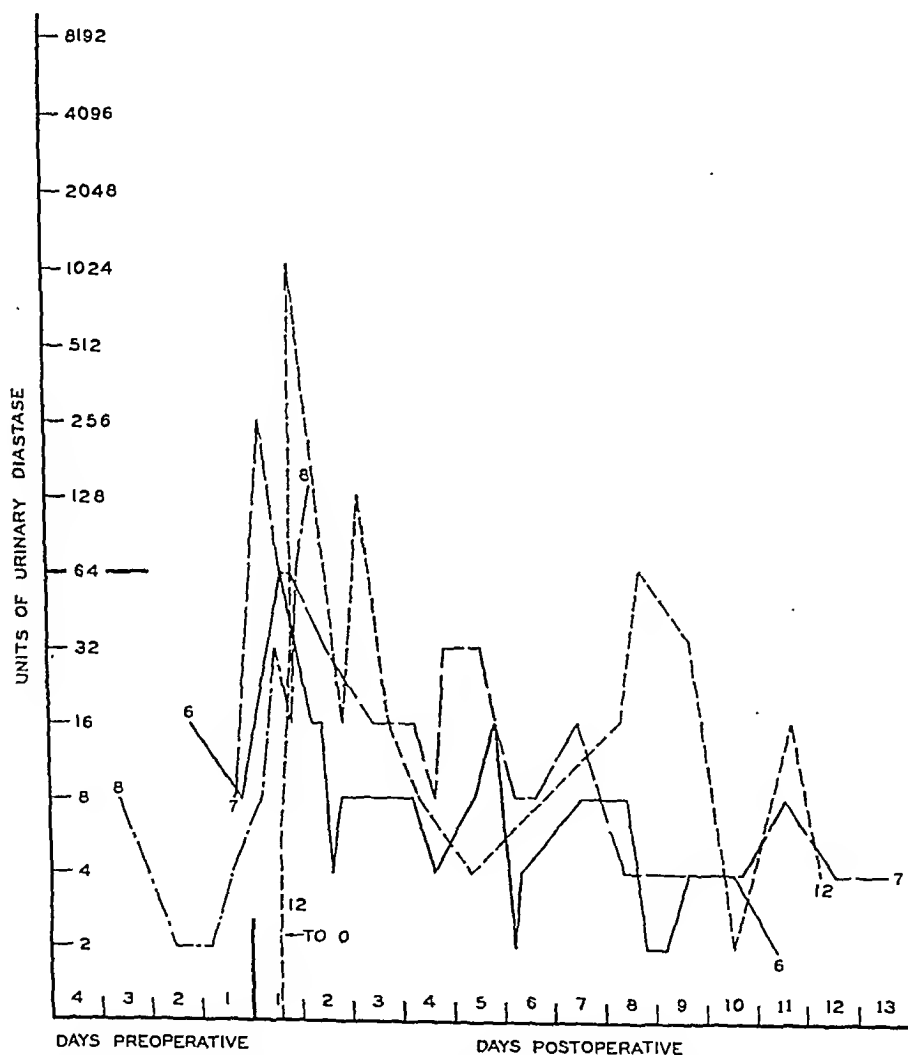


FIG. 1. Variations in urine diastase units in four selected dogs fed before operation at which pancreatic infarcts were experimentally produced. Each line refers to the animal designated by number.

Daily preoperative and frequent postoperative urine diastase tests were made by the method described above, with a total of 119 determinations. The results appear in table 1.

Opportunity for a satisfactory series of diastase studies was present in 11 of the 16 dogs. Of the five remaining animals, two (IX and XI) failed

to recover from the anesthesia and died within two hours after the operation. The other three (VIII, X and XVIII) died within 26 hours after the operation from generalized peritonitis resulting from perforation of infarcted areas in the duodenum.

Urine diastase values in 8 of the 11 animals in which an adequate number of specimens were examined were significantly elevated. Figures 1 and 2 illustrate these variations in those cases where elevated diastase

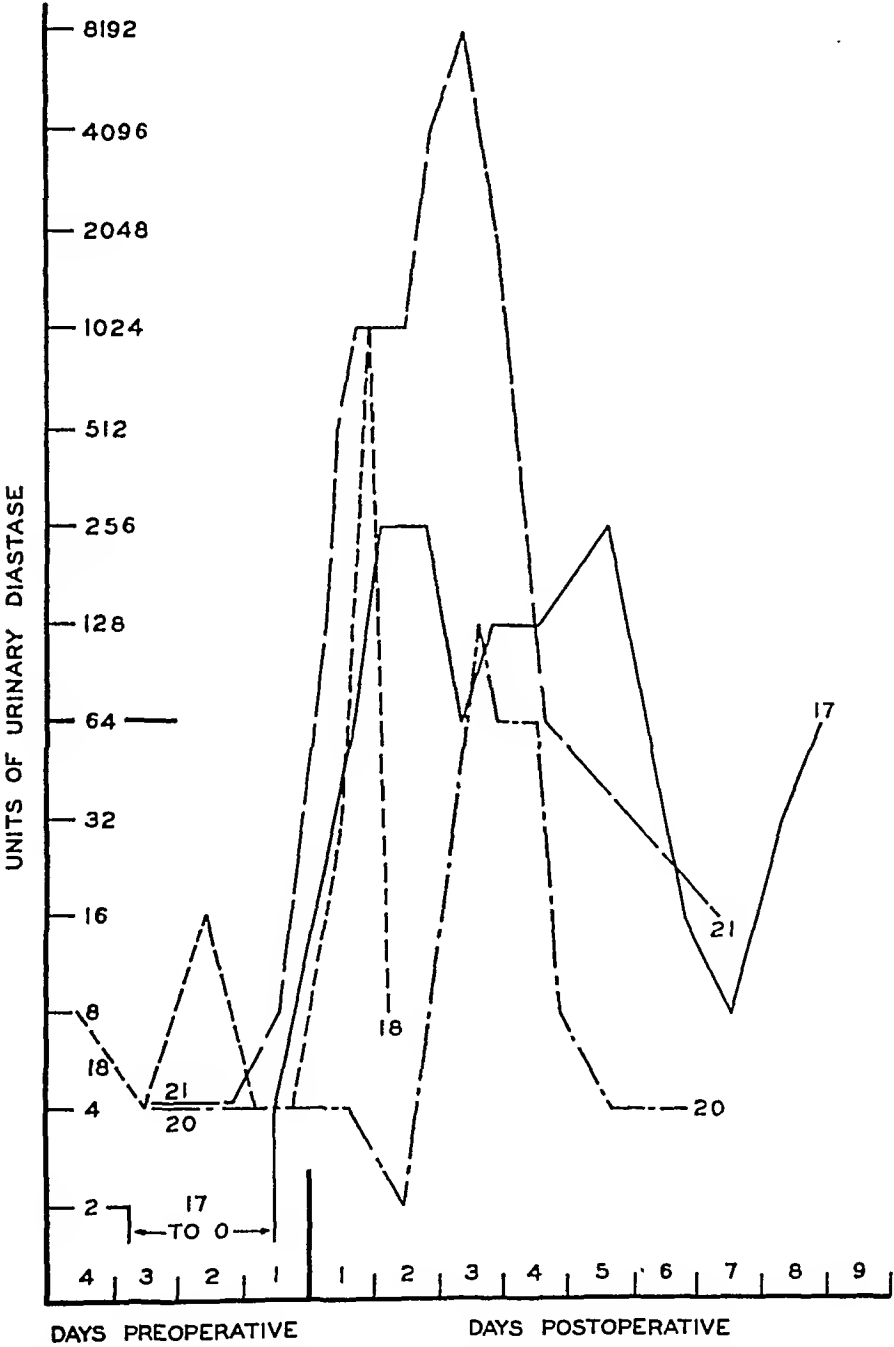


FIG. 2. Variations in urine diastase in four selected animals injected with acetyl- $\beta$ -methylcholine and physostigmine before production of pancreatic infarcts.

values were recorded. Postmortem examinations were made immediately after death and in all cases there were either gross or microscopic evidences of pancreatic necrosis. The areas of pancreatic necrosis produced by this embolic method did not extend to non-infarcted adjacent tissue. In the first group the dogs were sacrificed between the eleventh and the fifteenth day, and in the second group between the fifth and ninth day following operation.

These studies indicate that the urinary diastase test is a useful index to the presence of acute pancreatic necrosis. The viscosimetric methods used in studying blood diastase are more accurate. However, since the modified Wohlgemuth method requires very little apparatus, the reagents are easily prepared, and the time required is only 45 minutes, its more frequent use is recommended.

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# THE EFFECT AND RATE OF REMOVAL OF PYRUVIC ACID ADMINISTERED TO NORMAL PERSONS AND TO PATIENTS WITH AND WITHOUT "VITAMIN B DEFICIENCY" \*

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PYRUVIC acid has long been known as an intermediary product of carbohydrate metabolism. Nevertheless, there are but few reports on the pharmacological action of this substance in higher animals<sup>1, 2</sup> and, so far as we know, none on its action in human beings. Recently, considerable importance has been attached to pyruvic acid, chiefly through the rôle claimed for it in vitamin B<sub>1</sub> deficiencies. Peters and his coworkers<sup>3</sup> consider it an important, if not a specific substance in the "biochemical lesion" in experimental B<sub>1</sub> deficiency states, while Platt and Lu<sup>4</sup> report increased amounts of pyruvic acid in the blood, spinal fluid and urine of patients with "wet" beriberi. The work of these authors suggested the possibility that the lack of B<sub>1</sub> in the organism may disturb the normal metabolic pattern and result in the accumulation of abnormal intermediary metabolites, particularly of pyruvic acid, which in turn may produce the clinical symptoms and signs of vitamin deficiency.

Sherman and Elvehjem,<sup>5</sup> on the other hand, were unable to find increased amounts of bisulphite binding substances (including pyruvic acid) in the blood of B<sub>1</sub> avitaminotic chicks, although they did find increased amounts in the cloacal contents. They claim, however, that sodium pyruvate, when injected intravenously into these deficient birds, causes a prolonged rise in the blood bisulphite binding substances (B.B.S.), while in normal birds it causes no rise even immediately after injection. They conclude, therefore, that deficient birds are incapable of adequately removing pyruvic acid from the circulating blood and postulate that the defect lies in the intrinsic metabolism. De Jong<sup>6</sup> also has studied the B.B.S. of the blood of pigeons with B<sub>1</sub> deficiency. He found that polyneuritis usually developed before the rise of the B.B.S. and that the symptoms often disappeared while the B.B.S. remained elevated. Chronic polyneuritis was not associated with a rise in the B.B.S.

For the past two years an investigation has been in progress in this laboratory on the physiological and biochemical nature of the disturbances associated with vitamin B (B<sub>1</sub>) deficiencies in human beings and in rats.<sup>7, 8, 9, 10, 11, 12</sup> The present study of the pharmacology of pyruvic acid in normal and in diseased human subjects was undertaken in order (1) to determine

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the effect, the rate of removal and the excretion of sodium pyruvate injected intravenously in (a) normal subjects and (b) patients with various diseases, particularly vitamin B<sub>1</sub> deficiency; (2) to determine the absorption, action and excretion of sodium pyruvate administered orally; (3) to correlate, if possible, the pharmacological action of sodium pyruvate administered in single large doses with functional disturbances of vitamin B<sub>1</sub> deficiencies in human beings; and (4) to ascertain whether differences exist in the rate of removal of sodium pyruvate from the blood of normal human beings and of human beings with B<sub>1</sub> deficiency, similar to those reported in chicks by Sherman and Elvehjem.

### PROCEDURE

Pyruvic acid\* was neutralized with sodium hydroxide to pH 7.4, diluted with distilled water to make solutions containing 5 and 10 per cent pyruvic acid by volume, and again adjusted to pH 7.4. For intravenous use the 5 per cent solution was sterilized by passage through a Berkefeld filter. For oral use the 5 or 10 per cent solution was diluted just before administration with one-half volume of tomato juice in order to disguise the taste.

Subjects were studied in the fasting state and had been at rest for at least 30 minutes before observations were begun. The heart rate was counted by arterial palpation, by precordial auscultation or from the electrocardiogram; the arterial pressure was measured by arterial auscultation, using a mercury manometer; and electrocardiograms were taken with a string galvanometer, using the three standard leads and the cardiac apex lead. The rate and depth of respiration were noted, the tendon reflexes were tested, and signs and symptoms were searched for throughout the experiment. After control conditions were established blood and urine samples were obtained for chemical studies.

After numerous cautious trials it was decided to use for intravenous administration 100 ml. of 5 per cent sodium pyruvate, infused by gravity into the median cubital vein, allowing 3½ minutes for the injection. The amount and rate of injection were the same in all cases without regard to the body weight or to the state of the circulation. Immediately after the pyruvate had run in, a venous blood sample was taken from the opposite arm, the heart rate and arterial pressure were determined and an electrocardiogram was taken. Similar observations were made and blood samples were taken 5, 15, 30 and 60 minutes after injection. Urine samples were obtained as soon as possible following injection and every one or two hours thereafter.

In the experiments with oral administration the solution was taken in one dose. The heart rate and arterial pressure were determined at 10-minute intervals, and electrocardiograms and venous blood and urine samples taken at varying intervals, according to the changes expected.

\* Eastman Kodak Company "Research Grade."



Blood samples were analyzed for content of non-protein nitrogen and of glucose by the methods of Folin,<sup>13</sup> and for carbon dioxide capacity by the method of Van Slyke.<sup>14</sup> Pyruvic acid was determined indirectly by means of the bisulphite binding substances (B.B.S.), using a modification<sup>10</sup> of the method of Clift and Cook.<sup>15</sup> The increases in B.B.S. found after administration of pyruvate were interpreted as due to pyruvate.

Urine samples were measured and analyzed for acidity, sugar, acetone and diacetic acid by the routine methods, and for pyruvic acid by a modification<sup>16</sup> of the Simon-Piaux method.<sup>17</sup> In order to obtain the urine specimens during the experiments, subjects were given as much water as they would tolerate. Samples were collected until pyruvic acid had disappeared.

The electrocardiograms were examined and measured with particular attention to the duration of electrical systole, which was calculated by the formula,  $K = \frac{Q-T}{\sqrt{R-R}}$ .<sup>18</sup>

## SUBJECTS

Nine subjects were normal adults. Six received 100 ml. of 5 per cent sodium pyruvate intravenously, two received 100 ml. of 5 per cent pyruvate by mouth and three received 250 ml. of 10 per cent pyruvate by mouth.

Of 12 patients, six had no clinical evidence of vitamin B deficiency. Three of these had organic heart disease with varying degrees of congestive failure; two had liver disease with jaundice and one had severe diabetes mellitus, which was fairly well controlled with insulin. Five patients suffered with probable vitamin B<sub>1</sub> deficiency, varying in degree from severe "wet" (cardiovascular) beriberi to mild polyneuritis. There was one case of pellagra without neuritis.

All patients received the pyruvate intravenously and some, in addition, received it by mouth. In the "vitamin B deficient" patients, whenever possible the procedures were performed both before and after specific treatment in the form of crystalline vitamin B<sub>1</sub>.

## RESULTS

### *A. Intravenous Injection of 100 ml. of 5 Per Cent Sodium Pyruvate*

1. *Normal Subjects.* Table 1 summarizes the results of the six experiments on the normal group. Chart 1 shows graphically the results of a typical experiment, while chart 2A shows the blood B.B.S. curves for all experiments. It will be seen that there was essentially no effect on the heart rate or the blood pressure. Neither was there any noticeable change in respiratory rate or depth, or in the tendon reflexes. No symptoms were elicited except those that could be attributed to mild anxiety and excitement caused by the procedure, and occasionally a slight sensation of generalized "prickling" immediately after the injection, probably due to rapid infusion

TABLE I

NORMAL SUBJECTS:

Intravenous Infusion 100 ml. 5 Per Cent Sodium Pyruvate

Subject No.	Blood B.B.S. (mg./100 ml.)				Blood Sugar (mg./100 ml.)			Plasma CO <sub>2</sub> Capacity (vol. %)			Urine Pyruvic Acid	Electrocardiogram "K"	
	Initial Value	Change After Injection			Initial Value	Change After Injection		Initial Value	Change After Injection		No. Hrs. Positive	Change	Time of Change (min.)
		Immediately	5 min.	1 hour		5 min.	1 hour		5 min.	1 hour			
1	5.25	+10.95	+6.17	+0.50	96.6	+5.8	+1.4	54.5	+4.3	-1.4	6	+0.02	8
2	3.96	+ 9.64	+9.14	+0.53	95.3	-2.5	-4.6	64.4	+0.8	-2.2	5	+0.03	2
3	3.75	+11.05	+8.75	+2.50	87.7	0	-1.5	63.0	+1.9	-1.7	4	+0.03	2
4	3.88	+12.39	+6.47	+0.52	99.7	-2.4	-9.4	67.4	+6.9	—	4½	+0.04	2
5	5.27	+ 8.53	+9.73	+2.76	100.5	0	+4.7	—	—	—	6½	+0.06	2
6	4.16	+17.44	+7.19	-0.34	not fasting	—	—	—	—	—	2 +	—	—

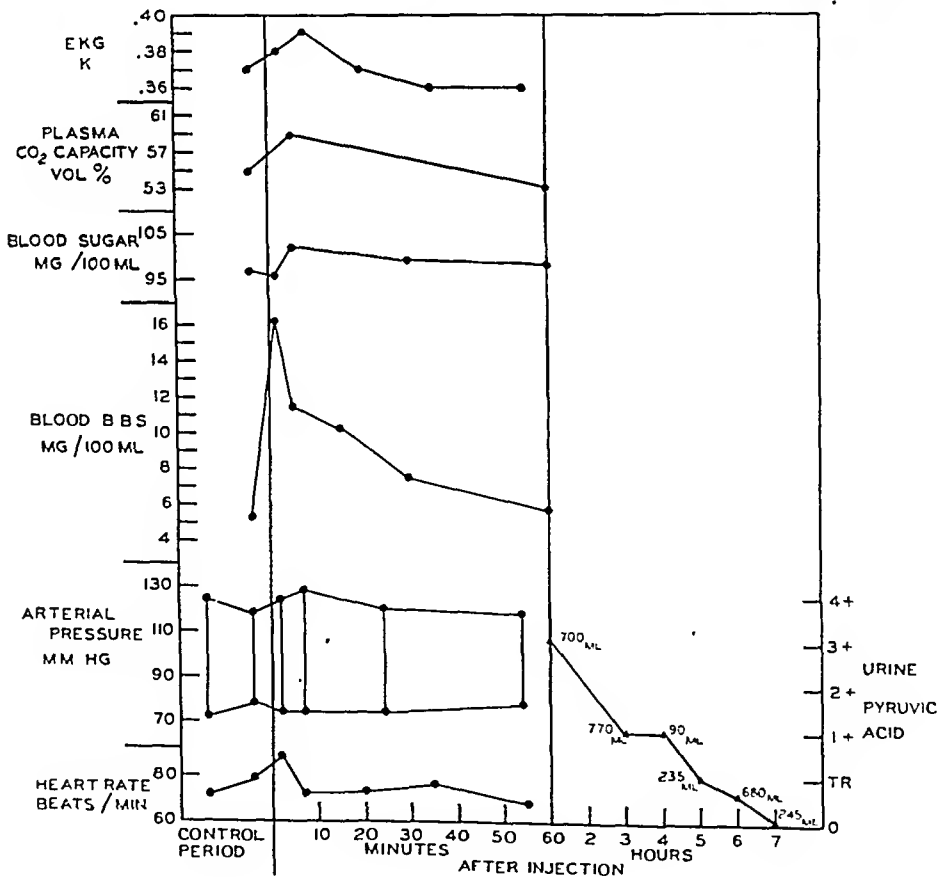


CHART 1. The effect of 100 ml. of 5 per cent sodium pyruvate, injected intravenously in a normal male subject, on the heart rate, arterial blood pressure, bisulphite binding substances (B.B.S.) in the blood, blood sugar, plasma carbon dioxide capacity, electrical systole of the heart (calculated as K), and pyruvic acid in the urine.

of the hypertonic solution. The B.B.S. rose sharply to a peak immediately after the injection, then decreased to practically its original level in the course of an hour. Pyruvic acid was found in the urine by qualitative test as early as 15 minutes after injection and for periods up to six hours, during the major part of which the B.B.S. level in the blood was essentially the same as during the control period. These results are interpreted to mean that sodium pyruvate is a low threshold substance for the human kidney, and that the qualitative test on the urine represents a fairly accurate gauge of

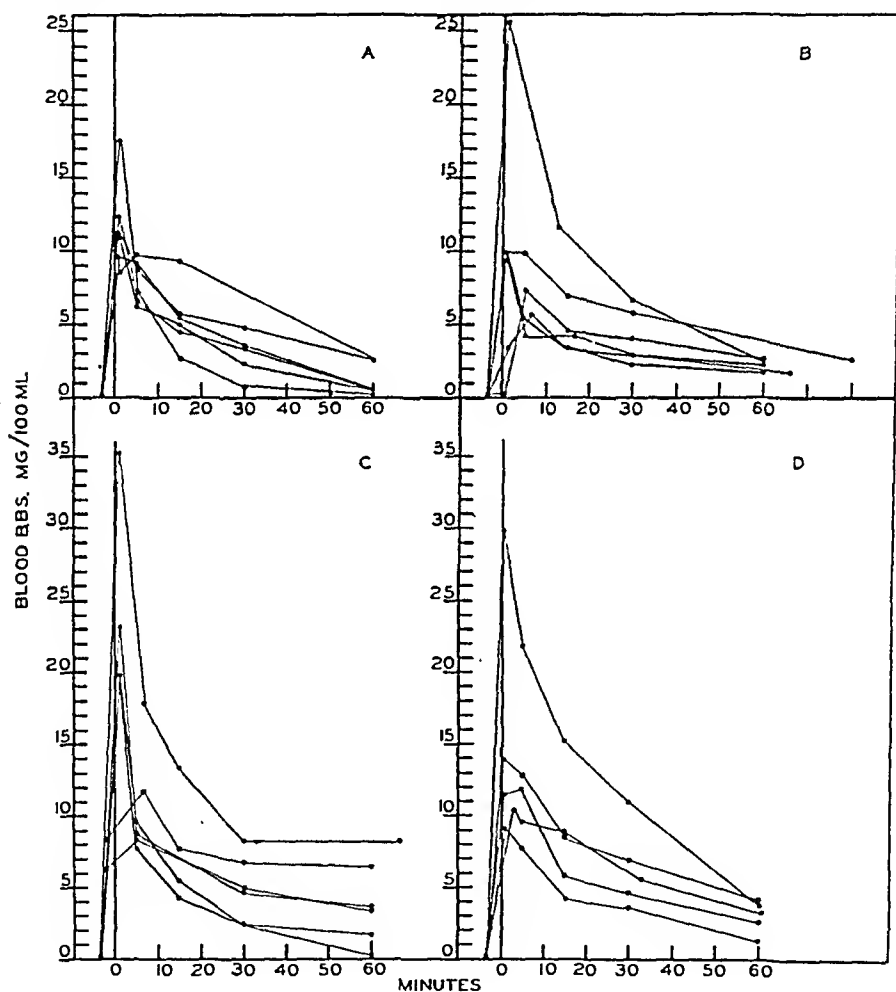


CHART 2. The effect of 100 ml. of 5 per cent sodium pyruvate injected intravenously on the bisulphite binding substances of the blood in (A) normal subjects; (B) patients without vitamin deficiency; (C) patients with "vitamin B deficiency," before treatment; and (D) patients with "vitamin B deficiency," after treatment.

the presence of appreciable amounts of pyruvate in the blood. The effect of pyruvate infusion on the blood sugar is regarded as inconsequential. There was no appreciable change in non-protein nitrogen. The carbon dioxide capacity usually increased 4 to 6 volumes per cent shortly after the injection, but returned to its previous level in an hour. This minor change was due to the administration of the sodium salt.

One of the uniform effects of sodium pyruvate was on the electrocardiograms, which showed lengthening of the Q-T interval, calculated as K, and minor but definite decrease in the amplitude of the T-waves. These changes appeared shortly after the injection and subsided in the course of an hour. Figure 1 shows the type of electrocardiographic changes produced. They are qualitatively the same as we have observed and as others<sup>10</sup> have reported following the intravenous and oral administration of sodium bicarbonate, and probably result in part from temporary alkalosis. In most cases the electrocardiographic changes were quantitatively greater after the

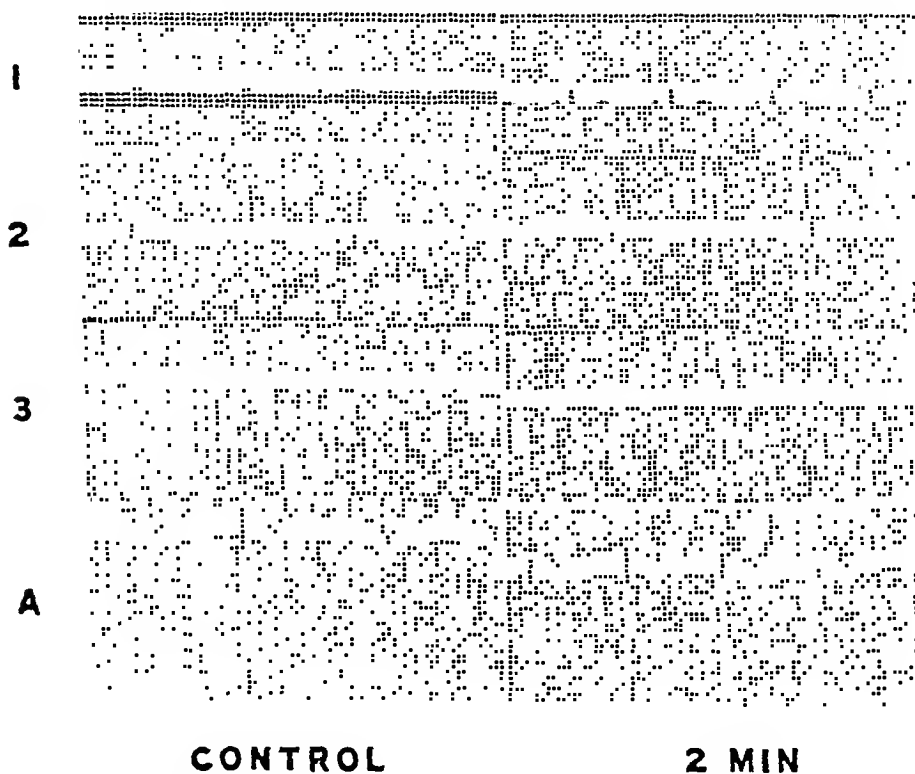


FIG. 1. Electrocardiogram of a normal subject before and two minutes after intravenous injection of 100 ml. of 5 per cent sodium pyruvate.

administration of sodium pyruvate than after the administration of comparable amounts of sodium bicarbonate.

2. *Patients Without Vitamin Deficiency.* Table 2 summarizes the results of intravenous injection of 100 ml. of 5 per cent sodium pyruvate in patients without vitamin deficiency. Chart 2B shows the blood B.B.S. curves. It will be seen that except for the greater initial rise in the patient with diabetes, who weighed only 100 pounds, and the slighter rises in those patients with edema or ascites, there were no distinctive differences from the normal controls. It may be that the physical factor of dilution of the pyruvate in a lesser or greater amount of body fluid caused the initial differences observed.

3. *Patients with "Vitamin B Deficiency."* Table 3A summarizes the

TABLE II  
 PATIENTS WITHOUT "VITAMIN B DEFICIENCY":  
 Intravenous Infusion 100 ml. 5 Per Cent Sodium Pyruvate

Patient No.	Diagnosis	Blood B.B.S. (mg./100 ml.)				Blood Sugar (mg./100 ml.)				Plasma CO <sub>2</sub> Capacity (vol. %)			Urine Pyruvic Acid	Electrocardiogram "K"	
		Initial Value	Change After Injection			Initial Value	Change After Injection		Initial Value	Change After Injection		No. Hrs. Positive		Change of Change	Time of Change (min.)
			Imme- diately	5 min.	1 hour		5 min.	1 hour		5 min.	1 hour				
1	Rheumatic aortic and mitral disease; moderate congestive failure	7.20	+ 9.95	+ 5.40	+1.77	115.9	-0.6	-2.9	51.5	+5.4	—	5½	(Auric. fibrillation)		
2	Luetic heart disease; aortic regurgitation; severe congestive failure	4.19	+ 3.35	+ 5.64	+2.18	72.0	0	+3.3	56.0	+2.2	-0.3	8+	"	"	
3	Rheumatic aortic disease; mild congestive failure	3.37	+ 0.19	+ 7.25	+2.49	95.3	-4.8	+0.7	61.1	+0.1	+2.3	9+	"	"	
4	Cirrhosis of liver; ascites; edema	4.07	+ 9.40	+ 4.02	+1.72	109.0	+0.5	-2.9	64.3	+0.5	—	7+	+0.06	2	
5	Arsphenamine hepatitis	4.50	+ 9.95	+ 9.87	+2.60 (80 min.)	100.5	+0.5	-3.1	—	—	—	6+	+0.03	2	
6	Diabetes mellitus	4.37	+25.51	+11.75 (12 min.)	+2.55	146.6	+9.4 (12 min.)	-8.6	62.2	+5.6 (12 min.)	—	4	+0.04	2	

TABLE III  
PATIENTS WITH "VITAMIN B DEFICIENCY":  
Intravenous Infusion 100 ml. 5 Per Cent Sodium Pyruvate

Patient No.	Diagnosis	Blood B.B.S. (mg./100 ml.)				Blood Sugar (mg./100 ml.)				Plasma CO <sub>2</sub> Capacity (vol. %)				Urine Pyruvic Acid	Electrocardiogram "K"		
		Initial Value	Change After Injection			Initial Value	Change After Injection			Initial Value	Change After Injection		No. Hrs. Positive		Change	Time of Change (min.)	
			Immediately	5 min.	1 hour		5 min.	1 hour	5 min.		1 hour						
A. Before Treatment																	
7	Severe "wet" (cardiovascular) beriberi	9.61	+23.09	+9.69	+1.67	131.8	+5.2	+12.1	49.5	+7.5	+5.2	8½ + + (?24)	-0.02	30			
8	Severe polyneuritis and psychosis; mild cardiovascular symptoms	3.97	+19.88	+8.86	+3.76	93.4	+3.7	-3.9	54.9	+8.3	+4.4	6	+0.03	6			
9	Severe polyneuritis; psychosis	5.79	+35.16	+17.81	+8.15	93.4	+1.6	+9.7	55.4	-2.0	-9.6	—	+0.02	9			
10	Mild polyneuritis	5.70	+19.85	+7.60	+0.28	89.9	+2.1	+1.4	64.0	-0.8	—	4½ +	+0.05	10			
11	Pellagra	6.60	+8.43	+11.77	+6.27	109.8	+14.8	+4.5	63.7	+2.9 (imm.)	+0.4 (15 min.)	10 +	+0.06	2			
12	Mild polyneuritis; psychosis	3.67	+6.10	+8.34	+3.43	110.5	-5.0	-1.5	57.3	-2.4	-2.8 (2 hrs.)	8	+0.04	2			
B. After Treatment																	
7	30 Days 910 mg. B <sub>1</sub> —10 days Orange juice, Vegex and cod liver oil—20 days	3.43	+10.37 (3 min.)	+9.62	+3.42	93.3	-11.0	+0.4	65.4	-0.9	+4.0	4½ + +	+0.01	53			
8	5 Days—350 mg. B <sub>1</sub>	5.09	+11.44	+11.86	+2.61	87.2	+0.5	+9.9	65.0	+6.2	+1.5	4½ + +	+0.05 +0.02	1 8			
9	2 Days—170 mg. B <sub>1</sub>	13.80	+29.85	+21.80	+3.60	73.5	+6.4	-2.7	51.6	+3.6	+4.2	—	+0.05	2			
10	5 Days—230 mg. B <sub>1</sub>	3.81	+9.05	+7.74	+1.23	91.8	-6.8	-0.2	59.3	+4.8	—	4½ +	+0.02	10			
11	6 Days—255 mg. B <sub>1</sub>	4.16	+13.89	+12.80	+4.12	113.0	+10.5	-0.8	68.8	+2.9	-1.7	10	+0.03	1 and 8			

effects of intravenous injection of 100 ml. of 5 per cent sodium pyruvate on patients with untreated "vitamin B deficiency." Table 3B shows the results in the same subjects after treatment with large parenteral doses (50 to 100 mg. a day) of crystalline vitamin B<sub>1</sub>. Charts 2C and 2D show the B.B.S. curves. There were no significant differences in the pharmacological action of sodium pyruvate on the "vitamin B deficient" patients and on the normal controls, as indicated either by symptoms or by the cardiovascular measurements taken. There were, however, some differences in the B.B.S. curves of these patients and of the normal controls, and slighter differences among the group before and after treatment. Some of the deficient patients showed a tendency to continued elevation in the B.B.S. at the end of one hour. The results in patient 9 require explanation. This patient was psychotic and could not be prevailed on to take fluids. The great rise in B.B.S. after injection and the continued high level at the end of the hour may have been partly due to dehydration. After treatment with vitamin B<sub>1</sub> her tolerance to pyruvate was essentially the same except that the B.B.S. at the end of the hour was not so high. The patient at this time had been given fluids by stomach tube and was less dehydrated. The immediate high rise in some of the deficient patients before treatment may have been due to the rapid circulation characteristic of this disease.<sup>8, 20</sup>

### *B. Oral Administration of Sodium Pyruvate*

Table 4 shows the effects of 100 ml. of 5 per cent sodium pyruvate and of 250 ml. of 10 per cent pyruvate by mouth. Except for the slower entrance into the blood stream by gastrointestinal absorption, there were no essential differences in the chemical findings from those in the intravenous experiments. In all cases with the large oral doses of 250 ml. of 10 per cent solution, however, there was a cathartic effect, characterized by moderate, watery diarrhea without severe abdominal cramps. In one subject (No. 8) this effect may have been great enough to interfere with absorption, but in the others the diarrhea did not become urgent until four hours had elapsed. In one subject (No. 7) dehydration from this cause was great enough to result in ketosis with acetone and diacetic acid in the urine after seven hours. The cathartic action continued for about 12 hours. The possibility that a large factor in the cathartic effect was simply the action of a hypertonic sodium solution could not be entirely ruled out. When the same amount of sodium pyruvate was given as a 2.5 per cent solution the cathartic effect was still present. In this case the large volume of fluid itself may, however, have contributed to this action. In the intravenous experiments no gastrointestinal symptoms were complained of, although the level of the pyruvate in the blood was usually much higher than that reached in the oral experiments.

TABLE IV  
Oral Administration of Sodium Pyruvate

Sub- ject No.	Diagnosis	Amount	Blood B.B.S. (mg./100 ml.)			Blood Sugar (mg./100 ml.)		Plasma CO <sub>2</sub> Capacity (vol. %)		Urine Pyruvic Acid		Electrocardiogram "K"			
			Initial Value	Change After Injection		Initial Value	Change After Injection	Initial Value	Change After Injection		No. Hrs. Positive	Time of Change (min.)	Change of Change (min.)		
				1 hour	2 hours				3 hours	1 hour				2 hours	
A. Normal Subjects															
7	No disease	100 ml. 5%	5.80	+3.05	+0.87	—	84.8	+ 0.3	— 2.5	57.6	+4.1	—	6½	+0.01	30
8	No disease	100 ml. 5%	4.51	+1.87	+0.66	+0.22	90.5	— 4.3	0	57.5	+5.1	+3.2	7	+0.02	63
7	No disease	250 ml. 10%	5.83	+5.35	+7.04	+6.45	104.8	—11.8	—11.4	59.4	—	+5.4	12	+0.06	120
8	No disease	250 ml. 10%	4.05	+7.93	+5.01	+7.79	79.5	+ 1.9	+15.8	59.6	—	+4.7	11½	+0.01	30
9	No disease	250 ml. 10%	3.43	+5.92	+7.30	+6.42	97.3	— 1.8	— 4.5	62.4	—	—0.6	10	+0.04	65
B. "Vitamin B Deficient" Patients After Treatment															
Pt. No.															
7	Beriberi	100 ml. 5%	5.13	+1.67 (75 min.)	+1.35	—	93.0	—	— 1.7	58.6	—	+2.6	7++	+0.01	60
12	Mild polyn neuritis; psychosis	100 ml. 5%	3.40	+2.27	+1.42	+0.06	104.2	+ 0.6	— 0.6	55.2	+5.1	—	9½	+0.02	33 125
7	Beriberi	250 ml. 10%	3.00	+2.75	+6.05	+7.70	104.2	—18.0	—18.9	67.4	+4.5	—	7++	+0.02	120
12	Mild polyn neuritis; psychosis	250 ml. 10%	4.34	+6.07	+7.34	+10.16	133.3	—23.5	—24.3	50.4	—	+10.0	10++	+0.01	65



## DISCUSSION

While pyruvic acid is an intermediary product of carbohydrate metabolism and represents a stage of oxidation at which theoretically catabolism results in formation of carbon dioxide and water, or anabolism produces lactic acid and glucose, it is usually not formed in the human body in amounts sufficient to raise the B.B.S. of the blood or to allow detection in the urine by sensitive qualitative test. Increased amounts of pyruvic acid have been reported, however, not only in normal subjects after strenuous exercise,<sup>21</sup> but also in patients with vitamin B<sub>1</sub> deficiency<sup>4, 10</sup> and in patients with diabetes mellitus.<sup>10, 22</sup> The problem of whether pyruvic acid can be utilized by the animal organism as an antiketogenic substitute for glucose or higher carbohydrates has stimulated investigations, with divergent results and conclusions.<sup>23, 24, 25, 26, 27, 28, 29</sup>

So far as may be judged from the acute experiments here reported, sodium pyruvate in the doses employed is essentially non-toxic for man. It produces no untoward symptoms, and with the exception of prolonging the period of electrical systole, probably due to transient alkalosis, it exerts no significant effects on the cardiovascular system or the blood chemistry. The cathartic action of the substance after oral administration is mild and of short duration. There is also experimental evidence that sodium pyruvate has such an action on the surviving gut.<sup>2, 30, 31, 32</sup> It may be that chronic excesses of pyruvate may produce these same effects to a greater degree, or may even result in other "toxic" reactions. The present study offers no direct evidence on this point.

With the method used, sharp differences were not found in the pyruvate "tolerance" of normal and of "B" avitaminotic human beings, such as Sherman and his coworkers reported in chicks. It may be that in normal human beings the ability to metabolize pyruvic acid is relatively slight in comparison with that in normal birds, so that any difficulty superimposed by vitamin deficiency is less apparent. The prolonged presence of pyruvic acid in the urine following intravenous infusion indicates that in normal man, at least, pyruvate is not rapidly metabolized. The amount and rate of the pyruvate infusions may therefore have been too great to allow clear-cut distinction of small differences. It is possible that with a different dosage of the pyruvate infusion sharper differences could be brought out. In the light of experience so far, the period during which the differences in metabolism become apparent seems to follow the first half hour after pyruvate injection. Thus not only the degree but also the duration of elevation of the blood pyruvate may be of significance in the comparison of the response of normal subjects with that of patients with B<sub>1</sub> deficiency.

The bisulphite binding capacity of the blood represents only an indirect measurement of pyruvic acid. It is possible that certain ketone bodies arising from the metabolism of pyruvate may bind bisulphite and contribute to the high values. Preliminary studies of the blood pyruvic acid measured directly support this possibility.<sup>33</sup>

## SUMMARY AND CONCLUSIONS

1. The pharmacological action of sodium pyruvate administered intravenously and orally in normal and diseased human beings has been studied.

2. Prolongation of the electrical systole and, following oral administration, mild catharsis, were the only constant effects of sodium pyruvate observed. The cardiac effect may be attributed to transient alkalosis, and the cathartic effect to hypertonicity of the solution administered.

3. Following pyruvate infusion in normal subjects the blood pyruvate, as measured by the bisulphite binding substances in the blood, rose sharply and then gradually fell toward its original level in the course of an hour. The non-protein nitrogen and the glucose content of the blood were not significantly altered.

4. As measured by sensitive qualitative test, pyruvic acid was excreted in the urine of normal subjects as soon as 15 minutes and as long as six hours after intravenous injection.

5. Some of the patients with "B" avitaminoses showed a tendency to a more prolonged elevation of the blood B.B.S. after intravenous injection of pyruvate. Clear-cut differences from the normal B.B.S. curves, however, were not apparent in every case of "vitamin B deficiency."

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# ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS— A SYSTEMIC DISEASE\*

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THE cutaneous lesions included in the term lupus erythematosus fall into the so-called erythema group of skin disorders. Since they are entirely distinct from lupus vulgaris, and since a tuberculous etiology has not been proved for them, it is unfortunate that the term "lupus" is part of their nomenclature. Many elaborate classifications have been proposed for this group of lesions, but most of them are needlessly complex, and are based upon more or less artificial morphologic variations. For our purposes it will be sufficient to divide them roughly into two large groups: (1) the chronic fixed or discoid type, and (2) an acute or subacute, often recurrent, type marked at times by widely disseminated and polymorphic lesions of the skin and mucous membranes, with constitutional symptoms, frequent widespread visceral involvement, and a variable clinical picture. This second type, the acute disseminated form of lupus erythematosus, is a disorder in which (as is so often the case in so-called skin diseases) the cutaneous lesions are merely part of a widespread general morbid process; it is so frequently associated with major visceral lesions and constitutional symptoms that it is of unusual importance to the internist and general practitioner. We wish to emphasize particularly those aspects of the disease which pertain to the field of internal medicine.

In our present state of knowledge the diagnosis must rest largely upon recognition of the skin lesions. A brief description of them and a comparison with the lesions of the chronic discoid form of lupus erythematosus is therefore necessary.

The chronic discoid form is much more common than the acute disseminated variety, and only rarely does it exhibit rapid extension or associated systemic manifestations. The lesions occur chiefly in parts exposed to light (face, nose, forehead, ears, dorsum of the hands, neck, etc.) and appear as scaling patches of varying size and color—they usually range from light pink to dark reddish brown. There is often hyperpigmentation; in long standing cases, marked atrophy and depigmentation of the skin occur. The lesions tend to extend slowly; the edges are sharply defined, and often infiltrated. The most characteristic feature of chronic lupus erythematosus, aside from its distribution on the malar prominences and the bridge of the nose, in a majority of cases, is the follicular dilatation and plugging seen in the active portion of the lesion, usually at the periphery.

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The initial change takes place in the hair follicles, and small erythematous comedone-like papules are seen. The follicular plugs are hard and horny, however, and cannot be expressed from the follicle as can ordinary comedones. Marked progress often requires months or years. Occasionally, especially after trauma, exposure to cold or actinic irradiation, tuberculin injections or gold therapy, the typical picture of the acute disseminated form may be engrafted upon the chronic discoid type.

In the acute disseminated variety the lesions are often polymorphic and are usually active. The entire gamut of lesions seen in the erythemas may be encountered; a relationship to erythema multiforme has been suggested.<sup>1</sup> The exposed areas of the body are the sites of predilection, but no cutaneous or mucous surface is immune. The typical initial lesion appears (usually on the face or nose) as a small, often impalpable, erythematous patch, which usually spreads rapidly. The so-called bat-wing or butterfly configuration across the cheeks and nose is characteristic. The affected area may rapidly extend to include the entire face, ears, neck and upper trunk. A wide variety of lesions may occur, simultaneously or in succession—livid edematous urticaria-like or erysipeloid areas, purpura, showers of petechiae, or reddish-brown to purple macules, eczematoid patches, bullae, telangiectases, crusted areas, or ulcers. The vermilion border of the lips may show edema, crusting, fissuring, or ulceration. The mucosal lesions usually begin as sharply defined patches of erythema, often followed by ulceration and purulent exudate; hemorrhagic lesions are common on the mucous surfaces. In one of our cases the first lesions observed were in the pharynx. While no single skin lesion is characteristic of all cases of acute lupus erythematosus, the most common and persistent change is a deeply erythematous swollen patch or plaque of varying size. When this occurs on the cheeks, the appearance may suggest erysipelas strongly, but the erythema is usually more livid, and progression of the margin less rapid. When remission occurs, marked atrophy and scarring or pigmentation may follow the subsidence of the cutaneous lesions.

A comparison of the chief clinical features of the acute disseminated and the chronic forms of lupus erythematosus is shown in table 1.

The clinical course of acute disseminated lupus erythematosus is extremely variable. Females are much more commonly affected than males and are especially susceptible between puberty and the menopause. The onset may be abrupt, and the course short and stormy, with a fatal termination in six or eight weeks. At the other extreme are cases marked by mild systemic reactions and prolonged remissions during which all cutaneous or visceral manifestations may disappear. Between these two extremes a wide variety of nosologic types is seen. The mortality of the disease is high: probably more than 90 per cent of cases end fatally within five years. A striking characteristic is the tendency for acute cutaneous and systemic manifestations to appear or recur after exposure to sun or ultraviolet light, roent-

gen-rays, insect bites, cold, or the intracutaneous injection of irritating substances such as tuberculin. The clinical course is at times dramatically unexpected—a patient who seems almost moribund may occasionally recover, or a tiny patch of facial erythema may initiate a fulminating and rapidly fatal illness. Renal failure, broncho-pneumonia, "toxemia," or terminal bacteremia are the commonest causes of death. The onset of the acute frank manifestations is sometimes preceded by a prolonged period of vague ill-health, often marked by grippe-like attacks, recurrent bouts of fever, malaise, purpuric phenomena, or arthralgia. A number of recurrent seasonal exacerbations of the skin lesions may precede the onset of systemic disturbances. One of our patients suffered an annual outbreak of facial lesions every summer for 24 years except one year when he was working at night. The final exacerbation ushered in a fatal phase of systemic involve-

TABLE I

Comparison Between Chronic Discoid and Acute Disseminated Forms of Lupus Erythematosus

<i>Chronic discoid</i>	<i>Acute disseminated</i>
Slow course of skin lesion (weeks or months).	More rapid course (days or weeks).
Lesions uniform	Lesions polymorphic
Scaling, moderately erythematous, pigmentation, atrophy, scarring.	Erythema, urticaria, diffuse swelling, purpura, petechiae, bullae.
Rarely systemic reaction or leukopenia.	Almost always severe systemic reaction and leukopenia.
Localization—tendency to light-exposed areas.	Localization—light-exposed or traumatized areas.
Mucous membrane lesions uncommon (except lips).	Mucous membrane lesions common (lips, mouth, pharynx, etc.).
Skin involvement—rarely extensive.	Involvement sometimes limited but usually extensive in acute phase.
Scarring almost always.	Often no scarring.
Treatment—moderately effective (bismuth, gold, ointments, local destructive measures, cautious removal of foci, ultraviolet light— <i>never</i> ; roentgen-ray—sometimes).	Treatment—highly ineffective (bismuth—maybe, gold—never; removal of foci, <i>never</i> during acute phase; ultraviolet light— <i>never</i> ; roentgen-ray— <i>never</i>

ment. Evidence of visceral involvement may precede the appearance of the skin lesions, or persist during periods of complete cutaneous remission. Fever, usually sustained and often high, is practically constant during the acute phases of the disease. Septic foci may develop in the viscera, lymph nodes or subcutaneous tissues, and their appearance often presages a terminal phase of the disease.

The cause of acute disseminated lupus erythematosus remains unknown. It has long been regarded by many writers as a manifestation of tuberculous infection or as an allergic response to tuberculo-toxin—this view appears to be based largely on the occasional finding of active tuberculous lesions in patients with the disease, upon the alleged recovery of tubercle bacilli from the blood stream in some cases, and upon the marked response which usually occurs after tuberculin inoculation. After reviewing the evidence, however, we agree with Keil <sup>2</sup> that proof of a tuberculous etiology is lacking,

and that the coincidence of active tuberculosis is not necessarily significant. An infectious or "toxic" etiology is strongly suggested by the clinical features of the disease. Various organisms have been recovered from the blood stream and focal lesions, including various streptococci, pneumococci, staphylococci, *B. pyocyaneus*, and others. There is no proof, however, that these have been other than coincidental or terminal invaders. Blood cultures are persistently sterile in the great majority of cases. It has been suggested that toxic products may be formed in the skin of certain persons, perhaps following exposure to actinic irradiation or various types of trauma, and that these noxae may, directly or indirectly, attack that part of the vascular system which bears the brunt of the disease. Skin sensitization to abnormal products of the reticulo-endothelial system, or sensitization to various metabolites (urea, hematoporphyrin, tyrosine, lactic acid, lymphocytic ferments, etc.) have been suggested as possible causes. Ludy and Corson<sup>3</sup> have recently reported the presence of hematoporphyrinuria and of lead in the skin in a series of cases observed in Philadelphia—they believe the disease to be increasing in frequency in this locality.

The histo-pathology of the disease appears to be compatible with the action of a "toxic," as distinguished from an infectious, agent. Keil<sup>4</sup> has recently advanced a concept of the disease which regards it as the expression of a widespread vascular disease process, of unknown etiology, involving chiefly the capillaries and to a lesser extent the arterioles and venules, with some extension into the perivascular spaces; such a concept would appear to agree with the clinical and pathological phenomena of the disease. This vascular predilection would explain the wide variety and the variability of visceral involvement, and the protean clinical nature of the disease. Lewis<sup>5</sup> has pointed out that the cutaneous areas most often affected are those in which the capillaries are of the "atonic" type (i.e., they fail to respond normally to the injection of vasoconstrictor substances). The characteristic vascular lesions have been described by Baehr, Klemperer, and Schiffrin<sup>6</sup> as consisting of (1) capillary dilatation with extravasation of blood and serum; (2) proliferative endothelial vascular lesions with thrombus formation; and (3) degenerative or necrotizing lesions in the walls of capillaries, arterioles and venules, often with hemorrhage into adjacent tissues. All three processes may be found in the same case, and in any part of the vascular tree. Hyaline capillary thrombi are characteristic and widespread.

More or less obscure relationships exist between acute disseminated lupus erythematosus and certain other syndromes:

(1) Thrombocytopenic purpura may precede, accompany, or follow the syndrome of acute erythematous lupus. In these cases the spleen is usually enlarged and the hematologic findings are typical. Keil<sup>7</sup> believes that the thrombocytopenia in such cases is due largely to the inclusion of platelets in the numerous hyaline thrombi which occur characteristically in the capillaries. Two cases are cited by him in which classical thrombocytopenic

purpura disappeared after splenectomy, with the development of fatal disseminated lupus erythematosus some months later. Thrombocytopenia, splenomegaly, and hemorrhagic phenomena are quite common in the course of the disease as more or less periodic phenomena.

(2) Raynaud's disease occasionally precedes or accompanies acute disseminated lupus erythematosus. Füllenbaum and Sosin<sup>8</sup> have recently reported such a case, in which necrosis of the spleen was found at necropsy. One of our patients, a 38 year old mulatto woman, presented the picture of Raynaud's disease for about 3 years, associated with occasional showers of tender petechiae on the hands and feet; she then developed a typical acute exacerbation of disseminated lupus erythematosus with abdominal pain, fever, petechiae, menorrhagia, splenomegaly, leukopenia, anemia, and thrombocytopenia. The lupus lesions were confined to the face, gums, ears, and scalp. The acute phase subsided, leaving her in a remission but with persistent anemia, leukopenia and thrombocytopenia, and showing occasional showers of petechiae. The skin lesions became pigmented and have responded to cautious local treatment. It is of some corollary interest that Völk<sup>9</sup> has reported the coincidence of periarteritis nodosa with acute disseminated lupus erythematosus.

(3) In 1895 Osler<sup>10</sup> reported under the name erythema exudativum multiforme a group of cases with polymorphic erythematous skin lesions associated with a variety of visceral lesions—acute nephritis in five cases, gastrointestinal or urinary bleeding in three and splenomegaly, endocarditis and pericarditis in others. It seems probable that some of those cases were identical with, or variants of, acute disseminated lupus erythematosus.

(4) The so-called Libman-Sacks syndrome<sup>11</sup> \* is at times accompanied by skin lesions identical with those of acute disseminated lupus erythematosus. This syndrome appears to present a somewhat indeterminate picture, resembling in certain aspects both rheumatic fever and subacute bacterial endocarditis, but differing from both in important respects. Its chief clinical characteristics include arthralgia, fever, white-centered petechiae, purpura, endocarditis and pericarditis, pleuropulmonary complications, anemia, leukopenia, splenomegaly, hepatomegaly, embolic glomerulonephritis and other embolic phenomena, and ulcerative mucosal lesions. Blood cultures remain sterile. The course may be prolonged but the mortality is high, death often resulting from cerebral disasters or intercurrent infection. The characteristic pathologic finding appears to be a form of verrucous valvular and mural endocarditis which will be described later. It seems beyond doubt that those cases described by Libman and Sacks with erythematous facial lesions were examples of acute disseminated lupus erythematosus with visceral involvement. Whether their other cases represent instances of the same disease without erythematous skin lesions must remain uncertain for the present.

\* Its existence as a nosologic entity has been questioned.<sup>12</sup>



Renal involvement is common, and renal failure is an important cause of death. The urinary findings are not consistently characteristic of any particular type of renal lesion, but merely indicate irritation or injury of the kidneys. The clinical picture may suggest any one of several kinds of kidney disease—glomerulo-nephritis, pyelo-nephritis, "diffuse" or "interstitial" nephritis, pyonephrosis, or tubular nephrosis. Baehr and his associates<sup>6</sup> reported that hypertension was uncommon in their cases; it was present, however, in four (one-third) of our patients. A variety of lesions has been described, including abscesses, tubular degeneration and necrosis, embolic glomerulitis, infarction, cloudy swelling, simple nephrosis, interstitial inflammatory change with cellular infiltration, and edema, "parenchymatous" and "hemorrhagic" nephritis, pyonephrosis, etc. Baehr, Klemperer and Schiffrin<sup>6</sup> have described what they believe to be the characteristic renal lesion of the disease, and one which they report having seen in no other condition with the possible exception of the kidney of eclampsia. This consists of a peculiar hyaline thickening of the walls of the glomerular capillaries, giving what they call the "wire-loop" appearance—these loops contain no amyloid or lipid material. Along with these changes they describe proliferative and thrombotic processes involving part or all of the glomerular vasculature; the picture may resemble that of the embolic glomerulo-nephritis seen in subacute bacterial endocarditis. Of our five cases which came to necropsy all showed significant glomerular lesions which will be discussed below. The clinical picture of nephritis may precede the onset of the cutaneous eruption, or persist when the skin lesions are in remission.

Equally important are the cardiac lesions which are found chiefly in the endocardium and pericardium. Dyspnea, tachycardia, and palpitation are common symptoms, but congestive failure occurs only occasionally, and even then is usually a late or terminal phenomenon. Electrocardiographic changes do not seem to be pathognomonic. Precordial murmurs are very common but in the presence of fever, anemia and tachycardia cannot be regarded as necessarily indicating endocarditis. The entire clinical picture may closely simulate bacterial endocarditis, and at times can be distinguished from it clinically only by the persistent sterility of blood cultures. The endocardial lesions may closely resemble those of acute rheumatic fever, but are usually bacteria-free on culture or section. The mitral and tricuspid valves are most frequently affected. In some cases evidence of healed valvular endocarditis has been found. Atypical verrucous lesions of the type described by Libman and Sacks<sup>11</sup> have been frequently reported. These are coarse, rather large, flat or wrinkled vegetations, frequently extending along the chordae tendineae and covering part of the mural endocardium. They are bacteria-free and on section are composed of hyaline-like thrombotic material, often with a superficial layer of freshly deposited platelets; they may be partially covered by endothelium. The subendocardial myo-

cardium may show degenerative changes, but Aschoff bodies and Bracht-Wachter lesions are said to be notably absent from the myocardium. Fibrinous pericarditis, with serous or serofibrinous effusion, is often found; pericardial frictions or the signs of effusion may give indication of such

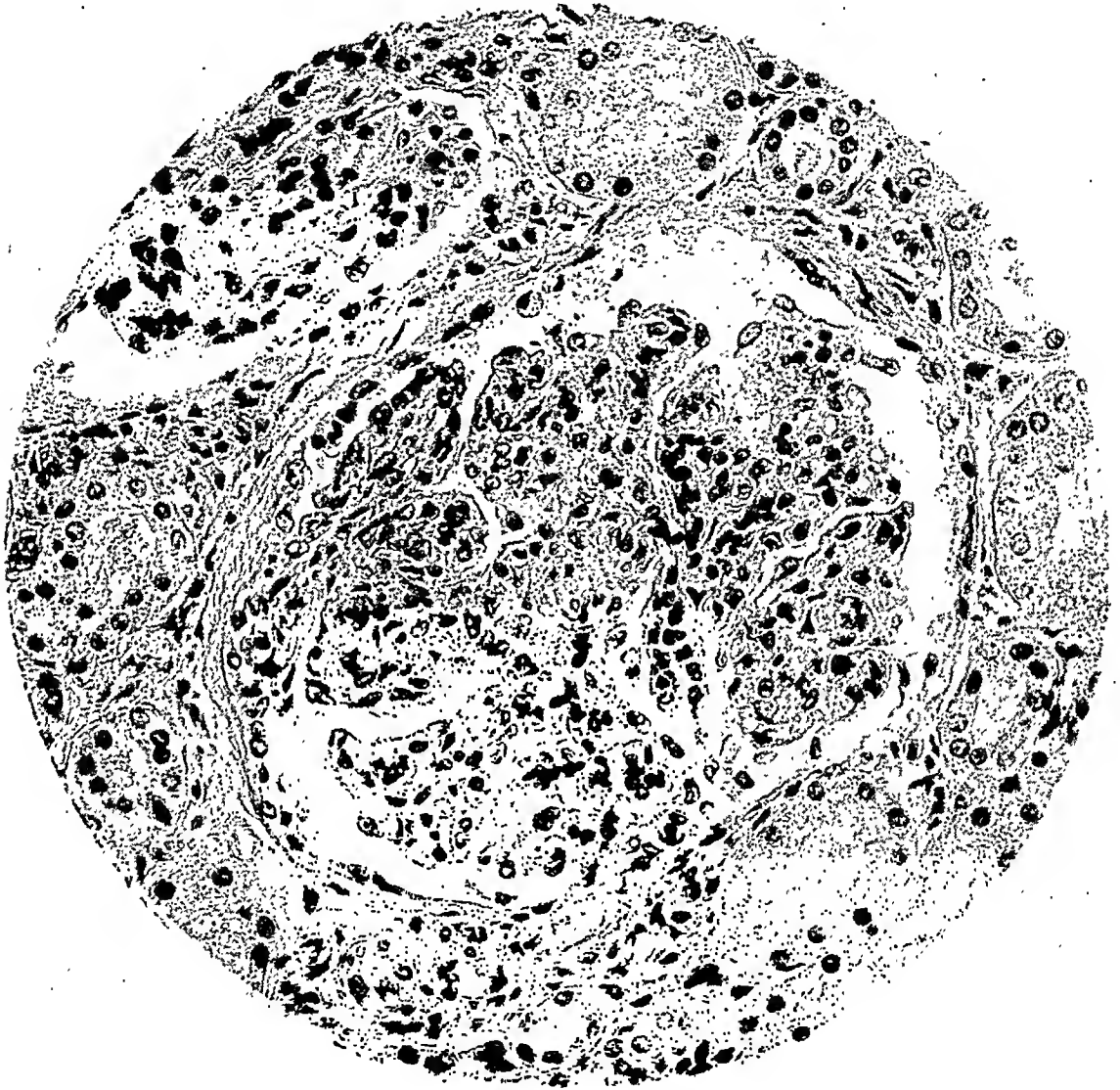


FIG. 1. Glomerular lesion (patient W. Z.) of acute disseminated lupus erythematosus. The glomerulus is large and richly cellular. In one area it has become fused or adherent to the capsular epithelium, which in that region shows moderate proliferation. Only two patent capillaries are seen and from them a few red cells have escaped into the capsular space. The remainder of the tuft is completely avascular.

processes during life. Endocardial lesions were found in only one of our five cases coming to necropsy, and in this instance the vegetations did not conform to the description of the Libman-Sacks variety. Another of our patients developed a large serous pericardial effusion but showed no sig-

nificant cardiac lesions at necropsy. Fibrinous pericarditis was found in one case.

Intra-ocular lesions are common. They include papilledema, sometimes with extension of the edema into and beneath the retina; retinal detachment and atrophy, guttate retinitis; perivascular exudates and hemorrhages, and choroidal degeneration. These lesions are not necessarily associated with renal disease, as they often occur in patients who present no evidence of kidney damage. They are probably a part of the widespread vascular disease.

Pulmonary complications are among the chief immediate causes of death. Bronchopneumonia, lobar pneumonia, abscess, gangrene, infarction and atelectasis are the most important. Severe tracheo-laryngitis is occasionally seen, and pleural effusion (usually serous, occasionally sero-fibrinous or purulent) is very common. Active pulmonary or tracheo-bronchial lymph node tuberculosis does not seem to occur with significant frequency.

Lymphadenopathy is likewise common, and may precede the appearance of the eruption. Both the superficial and deep lymphatic chains may be affected by suppurative or necrotizing changes. Active tuberculous lymphadenitis has been found in a number of cases.

Arthralgia may precede or accompany the eruption and systemic phases of the disease, and is sometimes mistaken for a symptom of rheumatic fever or infectious arthritis. Joint deformities have been reported. Serous, bloody, or purulent synovial effusions are common, and periarticular swelling occasionally occurs. The large joints appear to be more commonly affected.

Effusion may occur in any of the serous cavities. Reference has already been made to pleural and pericardial effusion; peritoneal effusion is less common, but may produce acute or subacute abdominal symptoms. This is also true of the mucosal lesions occurring in the gastrointestinal tract, and of embolic or thrombotic phenomena in the mesenteric circulation. Such processes may simulate acute abdominal emergencies so closely as to lead to unnecessary surgical exploration.

The liver is often enlarged as a result of cloudy swelling, acute congestion, pylephlebitis or abscesses. Jaundice is an occasional complication. The spleen frequently enlarges likewise, and may show parenchymatous degeneration, acute splenitis, acute congestion, necrosis with arteriolar obliteration, abscess, infarction, or perisplenitis. The typical clinical picture of acute splenic infarction may be recognizable, including the appearance of a perisplenic friction rub.

The principal feature of the blood picture is the leukopenia which is seen at some time in the course of the great majority of cases. In our experience this has been due to a roughly uniform reduction in the number of all the leukocyte forms, with perhaps some tendency toward a relative neutrophilic increase. The lymphocytosis mentioned by some writers<sup>3</sup> was

not evident in our cases. The leukopenia may persist during remissions. When leukocytosis occurs, it is seldom marked and usually accompanies some septic complication or the terminal phase of the disease. One of our patients showed occasional eosinophilia up to 8 per cent. Thrombocytopenia is well recognized, especially as part of the purpuric syndrome previously mentioned. During remissions the platelets may rise to normal levels. In the acute purpuric phases coagulation time may be prolonged and clot retraction may be abnormal. The sedimentation rate of the erythrocytes is frequently increased, and this increase may persist during clinical remissions. Hemorrhagic changes and a leukoblastic reaction in the bone marrow have been reported.<sup>13</sup>

The ulcerative lesions which occur in the mucosa of the gastrointestinal tract (including the mouth and pharynx), vagina and bladder may give rise to severe hemorrhage. Hematemesis occurred in two of our cases, and hemorrhagic cystitis was also present in one.

The significant data relating to 12 cases of acute disseminated lupus erythematosus which we have observed in the past six years are summarized in table 2. Eleven of these patients were seen at the Hospital of the University of Pennsylvania, and one was seen at the Children's Hospital of Philadelphia. It will be seen that nine patients were females, the majority being in the second and fourth decades. Nine patients have died, two are in remissions, and one shows a mild recurrence of the skin lesions without any evidence of systemic involvement at present. Pneumonia, renal failure, and "toxemia" were the chief causes of death. The uniform sterility of blood cultures, in the 10 cases in which this procedure was carried out, is striking. In the five patients who came to necropsy no evidence of active tuberculosis was found. Clinical or postmortem evidence of renal irritation or damage was present in 10 cases—hypertension occurred in four of these. Vascular lesions of varying degree in the glomeruli, similar to those described by Baehr and his associates, were found in all of the five patients coming to necropsy (hypertension had been present in none of them). The "wire-loop" appearance of the capillaries, focal necroses, and varying degrees of cellular proliferation, avascularity and ischemia were the chief characteristics. The inflammatory lesions of the glomeruli varied in severity from partial involvement of occasional tufts to well marked diffuse glomerulo-nephritis. The most frequent finding was rich cellularity and fusion of the component capillaries in isolated glomerular lobules; in some instances this was associated with foci of necrosis. No gross characteristic changes were seen in the kidneys. The pathological diagnosis was focal glomerulo-nephritis in three cases, and atypical diffuse glomerulo-nephritis in two. Cloudy swelling, abscess, and simple nephrosis were other changes found.\*

The high incidence of leukopenia in our series confirms the consensus in

\* The glomerular lesions were found only on reëxamination of the necropsy material, and were not reported in our original presentation.

TABLE II  
Summary of Twelve Cases of Acute Disseminated Lupus Erythematosus

Case	Age	Sex	Color	Result	Duration	Remissions	Cause of Death	Systemic Manifestations	Hemogram					Comment
									W.B.C. (Thousands)	Hb. (per cent)	R.B.C. (Millions)	Platelets (Thousands)	Sed. Rate R.B.C.	
A. C.	20	F.	White (Italian)	Death	3 mos.	None	"Toxemia," Bron- chopneumonia	Bronchopneumonia. Serous pleural and pericardial effu- sions. Adenopathy. Arthral- gia. Focal glomerulo-nephri- tis.*	3.9 to 6.6	50 to 78	3.2 to 4.1	140 to 425	+	Renal function normal. Large serous pericardial effusion. Hemolytic <i>Streptococcus au-</i> <i>reus</i> recovered from bone mar- row during life.
G. D.	30	F.	White	Death	4 years	4 or 5	Bronchopneumonia	Arthralgia. Bronchopneumonia and pleurisy. Acute veru- cous endocarditis (initial); cardiac hypertrophy. Septic splenitis with splenomegaly. Ulcers on palate and nasal septum. Focal glomerulo- nephritis.*	2.9 to 13+	48 to 87	3.0 to 3.9	204 to 380	+	Arthralgia with each exacerbation. Marked albuminuria. Exacerbations usually occur- red in summer.
W. Z.	25	M.	White	Death	3 mos.	None	Bronchopneumonia	Hemorrhagic splenitis. Fatty degeneration of the liver. Bronchopneumonia. Atypi- cal diffuse glomerulo-nephri- tis.*	2.3 to 10+	72 to 92	4.1 to 4.4	.....	....	Marked albuminuria. Termi- nal slight azotemia. Loss of 27 pounds. Glomerular le- sions very marked.
G. E.	39	M.	White	Death	24 years. (Auto terminal phase 23 months)	24 (Winter remissions)	Renal failure Bronchopneumonia	Acute splenic tumor. Fatty infiltration of liver. Bron- chopneumonia. Fibrous pericarditis and myocardial degeneration. Atypical dif- fuse glomerulo-nephritis.*	7.8 to 21+	68 to 85	4.1	320	+	Annual summer exacerbation of skin lesions for 24 years (missed one summer when he did night work). Albumin- uria and terminal azotemia.
E. C.	16	F.	White	Death	8 weeks	None	"Toxemia" Bronchopneumonia	Bronchopneumonia, atelectasis, pleural effusion. Multiple liver abscesses. Solitary renal ab- scess; focal glomerulo-nephri- tis. Hemorrhagic cystitis. Stomatitis. Epicarditis.*	3.0 to 7.5	52 to 81	2.6 to 4.3	.....	....	Fulminating course with rapid spread of skin lesions. Hem- atemesia. Stomatitis. Renal function moderately reduced. Hypochloremia.
E. E.	19	F.	White	Death	Uncertain, at least 1 year	Probably 2 (Partial)	Unknown	Arthralgia. Adenopathy. Pap- illedema. Pericarditis. Pleurisy with effusion. En- largement of liver and spleen. Albuminuria. Hypertension.	1.3 to 10.5	54 to 100	3.2 to 4.8	.....	....	Acute exacerbation after cau- terization of cervix. Renal function moderately impaired. Hypoproteinemia. Died af- ter leaving hospital.

TABLE II—Continued

Case	Age	Sex	Color	Result	Duration	Remissions	Cause of Death	Systemic Manifestations	Hemogram					Comment
									W.B.C. (Thousands)	Hb. (per cent)	R.B.C. (Millions)	Platelets (Thousands)	Sed. Rate R.B.C.	
M. D.	64	F.	White	Death	6 mos.	None	Renal failure	Clinical picture of severe nephritis, with vomiting, hypertension, azotemia, albuminuria, cylindruria, reduction of urinary specific gravity, hypoproteinemia.	4.0 to 5.2	64 to 67	2.6 to 3.6	.....	....	Renal failure dominated the clinical picture. Died after leaving hospital.
V. A.	38	F.	Mulatto	In remission	Uncertain, probably 2 or 3 years	Two	.....	Abdominal pain, purpura, petechiae, cardiac murmurs, splenomegaly, menorrhagia, pneumonia(?) and pleural effusion, albuminuria and cylindruria. Moderate reduction of renal function.	4.5 to 13.9	48 to 82	2.6 to 4.2	80 to 308	+	Raynaud's symptoms for 2 years + prior to onset of acute phase. Two exacerbations with thrombocytopenic purpura and severe abdominal pain. Now in remission with anemia, leukopenia and increased sedimentation rate of red cells.
H. K.	17	F.	White	Death	5 mos.	None	"Toxemia"	Papilledema and retinitis. Arthralgia, purpura, hypertension, albuminuria, hematuria and cylindruria. Splenic infarction. Pleural and peritoneal effusions.	4.3 to 15.0+	28 to 67	1.7 to 4.0	145 to 281	....	Exacerbation after exposure to sunlight. Arthralgia, edema and purpura on legs were earliest symptoms.
M. B.	34	M.	White	Death	1 year	One	Unknown	Arthralgia. Adenopathy. Bronchopneumonia. Systolic mitral murmur. Hypertension. Albuminuria. Ulcerative sore throat.	5.0 to 14.0+	60 to 100	3.7 to 5.1	128 to 323	....	Exacerbation after ultraviolet therapy. Lesions on ears preceded acute phase by about 9 months.
A. B.	25	F.	White	Still alive. (Recurrence)	3 years	One, lasting about 2 years	.....	Cervical lymphadenopathy. No cardiac, renal, or pulmonary manifestations.	3.4 to 6.0	82 to 88	4.3	115 to 202	Normal	Increasing sensitivity to sunlight, with annual summer erythema for 4 years before acute phase.
G. F.†	11	F.	White	Remission	9 mos.	Two	.....	Acute otitis. Faint systolic apical murmur.	4.0 to 5.9	76 to 80	4.1 to 4.2	256	+	In complete cutaneous remission for 4 years when last seen, but still has leukopenia, anemia and increased sedimentation rate. Some delay of development of secondary sex characters.

\* Confirmed by necropsy.

† Terminal.

‡ Blood culture not done—blood cultures sterile in all other cases.

the literature. Eleven of our patients exhibited leukopenia at some time during their disease; this persisted during most of the period of observation in the majority of cases, although leukocytosis occurred sporadically in seven instances.

The importance of light-sensitivity in this disease is borne out by the fact that six of our patients developed their initial eruption, or a cutaneous exacerbation, immediately after exposure to sun- or ultra-violet light. Three patients gave histories indicating abnormal sensitivity to sunlight for months or years prior to the onset of the acute phase of their disease.

It may properly be asked whether the visceral lesions of the acute disseminated lupus erythematosus syndrome may exist in the complete absence of cutaneous lesions—whether there may be such an entity as *lupus sine lupo*. The description of some of the cases without skin lesions reported by Baehr<sup>14</sup> and by Libman and Sacks<sup>11</sup> strongly suggests that they may have been examples of such a syndrome, but until the disease can be reproduced experimentally or until its cause is known, it seems unlikely that the existence of such a non-eruptive form can be translated from an hypothesis into a fact. Meantime, however, it would seem proper to consider the possibility of such an entity in a patient with fever, leukopenia, petechiae or purpura, embolic phenomena, arthralgia, evidence of endocarditis, pericarditis, renal injury, pleural effusion, and persistently sterile blood cultures.

The high mortality of acute disseminated lupus erythematosus is ample evidence of the inefficacy of treatment. A large number of therapeutic agents have been employed, none of which is consistently effective. It is perhaps more important to know what to avoid than what to use in treatment. The dangers of exposure to sunlight (even when filtered through glass) and ultra-violet light have previously been mentioned; patients should carefully avoid such exposure even when in remission, or if suffering from the chronic form of lupus erythematosus. In the treatment of the acute phase the patient should be kept in a darkened room. Too frequent exposure to roentgen-rays should be avoided. The removal of focal infection is often followed by severe exacerbations, and should if possible be avoided during acute phases. In the chronic form of the disease, or during remissions, foci of infection should be attacked with great caution, not more than one focus being removed at a time. Likewise the injection of tuberculin into or beneath the skin may be followed by a serious exacerbation, and should be avoided. The use of gold salts during acute phases of the disease, or in remissions, is highly dangerous.

The use of protective creams or ointments, especially those containing quinine, is often helpful. Other local measures for the softening or removal of crusts, wet dressings for septic foci in the skin, the treatment of decubitus ulcers, oral hygiene, etc. are of course frequently indicated. General therapeutic agents which have been tried include blood transfusions, whole blood injections intramuscularly, pentose nucleotide, lyophilized convalescent scarlet fever serum, polyvalent anti-streptococcic serum, sulph-

anilamide, liver extract, vitamin B concentrate, quinine, intramuscular bismuth injections and plasmochin by mouth or intravenously. Most of these have been employed in our cases with no evidence of any specific effect. When remissions occur they usually seem to do so spontaneously.

In summary, it may again be emphasized that acute disseminated lupus erythematosus is a systemic disease of unknown cause, with extensive and polymorphic cutaneous and visceral lesions apparently due to widespread vascular damage. It occurs chiefly in young or middle aged white females, many of the subjects being abnormally light-sensitive. The prognosis is grave. The clinical picture, while variable, is nevertheless marked by certain prominent features which, in the presence of the skin lesions, should in most cases lead to a correct diagnosis. The occurrence of leukopenia and certain lesions of the renal glomeruli appear to be strikingly constant features. The disease is of importance to the internist and the general practitioner as well as to the dermatologist. By its early recognition and the avoidance of certain dangerous procedures, especially exposure to sun and ultraviolet light, serious or even fatal exacerbations may at times be prevented.

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# THE AGING PROCESS: A MEDICAL-SOCIAL PROBLEM \*

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"Now that the average length of human life is increased and there are more and more old people, a fact that marks the triumph of science and civilization, there is more need of studying them, just as in recent decades children have been studied, for medically, at least after the climacteric, they constitute a class in the community that is somewhat alien, its intrinsic nature but little known, and the services it was meant to render but little utilized."

G. STANLEY HALL,<sup>1</sup> in *Senescence*.

## INTRODUCTION

THE desire for long life and a delay of the onset of senile changes is accepted as a normal and legitimate objective. Until recently, however, there has been little scientific concern for the factors contributing to human longevity. Indeed, the distinctive needs, somatic and psychic, have been practically unconsidered. The older the man, the more he must depend upon his own hygienic sagacity for health and long life. It has been said that physicians know little about old age and its problems. Certainly, Geriatrics has not received as systematic consideration and analysis as have the problems of Pediatrics.<sup>2</sup> While scholars have written of the philosophical aspects ever since, and even before Cicero wrote "De Senectute,"<sup>3</sup> the scientific study of Geriatrics is of comparatively recent origin.

Alexis Carrel, a short time ago, made an appeal for the endowment of an institute, dedicated to the study of the aging process. At the present time,

\* Delivered before the American College of Physicians, New York City, April 4, 1938.

one of the great philanthropic foundations is collecting the important data on the aging process, and several notable investigators are now directing their attention to the aging problem.<sup>4</sup> Not only should youth be served and conserved, but likewise the values of later life need be recognized, studied, and more completely utilized. The masses of mankind are notoriously improvident of the future and in mid life the decrepitude of old age appears remote and uncertain.

The onward march of medical science has controlled the ravages of the early years, permitting more and more individuals to attain maturity.

And now, the chances of reaching the later years of life are better than ever before. Therefore, a consideration of the aging process as a medical, and from the broader point of view a social problem, is of practical importance.

#### THE INCREASE IN LIFE EXPECTANCY .

One of the triumphs of modern medicine is the marked increase in life expectancy. In the sixteenth century, an infant had a life expectancy of 21 years. In the seventeenth century, this had increased to 26 years. By the middle of the eighteenth century, it was 34 years, and in the latter part of the nineteenth century it had extended upward to 40 years. In 1930,<sup>5</sup> male infants had an expectancy of 60 to 65 years and females from 62 to 68 years.

Expectancy of life in foreign countries, in 1930:

	Males	Females
Denmark .....	60.9	62.6
Sweden .....	61.10	63.33
Holland .....	61.09	63.5
Norway .....	60.98	63.84
New Zealand .....	65.04	67.88

Expectancy of life in the United States, 1930:

Iowa .....	65.90
Kansas .....	66.06
Minnesota .....	65.22
Nebraska .....	65.82
North Dakota .....	65.95
Oklahoma .....	65.42
Oregon .....	65.45
South Dakota (males 64.38) .....	66.81
Washington .....	65.41
United States (males 59.31) .....	62.83
Negroes (all told) .....	49.53

It is reasonable to presume that gain in expectancy of life will continue in the future, although certainly, it will not be at such a rapid rate. By 1960, a boy may expect to live approximately 75 years, and a girl may reach 80 years or more. The explanation for this spectacular increase in life, for such it is, resides in the increase in knowledge of both bacterial and parasitic diseases, as well as a clearer understanding of human nutrition.

Control of such diseases as bubonic plague, the black death of the Middle Ages, yellow fever, diphtheria, small-pox, typhoid fever, whooping cough and measles, have saved millions of lives of little ones. On the other hand, there has been little, if any, increase in the number of centenarians.

The 1930 census in this country showed that there were 3,964 persons 100 or more years of age.<sup>6</sup> Of these, it was recorded that 2,647 were Negroes. This seems incredible but may be possible on the basis of a placid, even temperament and an indisposition to be influenced by the nervous drive of modern existence.

More people, however, do reach middle life than at any other time in the history of the world. Once having attained the later years, there is no significant increase in the life span.

#### ACCIDENTS AND LONGEVITY

A systematic study of the various forces that injure and destroy life, with a corresponding listing of known precautions to avoid them, should be one of the objectives in a consideration of the prolongation of life. The difficulty with this approach, as pointed out by Malisoff, is that the solutions recommended are likely to be quite superficial. The strength of this approach, however, resides in the fact that many superficial facts taken together, may amount to something after all.

The most common and readily remediable cause of interruption or cessation of human life is the large number of accidents which maim or destroy human form, either in the home, on the highway, or in the factory. According to insurance statistics, the amazing number of 104,000 persons died accidentally in the United States in 1937. This figure was 6 per cent below that for 1936, although, with the exception of that year's total, it was the country's highest for fatal accidents.

One of the surest ways to keep from growing old is apparently to get mixed up in the traffic jamboree. The following is a list of automobile fatalities from the years 1932 to 1937 inclusive<sup>7</sup>:

	Deaths from Accidents
1932 .....	29,451
1933 .....	31,363
1934 .....	36,101
1935 .....	36,369
1936 .....	37,800
1937 .....	39,700

These statistics are mentioned in passing merely to emphasize the large number involved, and to suggest that individual and social caution and regulation can readily reduce this number.

#### COMMUNICABLE DISEASES, INFECTIONS AND LONGEVITY

Less than a century ago, communicable diseases accounted for approximately 900 deaths per 100,000 population per year. In order of their fre-

quency as a cause of death, these diseases were: tuberculosis, pneumonia, scarlet-fever, typhoid, diphtheria, whooping cough, measles and small pox. Except for tuberculosis and pneumonia, all of the other infections have been almost entirely eliminated as factors of importance. Less than 4 per 100,000 population died of these other infections during 1936, whereas, in the years 1856 to 1865, they caused on an average, over 300 deaths per 100,000 per year.<sup>8</sup> Preventive medicine is assuming a position of greater and greater importance in the medical-social sphere.

In the years 1856 to 1865, the average death rate from tuberculosis was 446 per 100,000 population, whereas in recent years it has averaged around 40 per 100,000 population—a decrease of more than 90 per cent. With a better understanding of the epidemiology and social and individual factors involved in the spread of tuberculosis, and a more enlightened policy on the part of the communities, tuberculosis as a cause of death will rapidly recede in importance.

Pneumonia had an average death rate of 107 per 100,000 population for the decade 1856 to 1865. In 1936, it was 96 per 100,000 population, representing a decrease of only 10 per cent. Today, however, pneumonia is more clearly understood, so far as its etiology, epidemiology, diagnosis and treatment are concerned. It is susceptible to control on a broad, geographical plan. Early diagnosis and adequate treatment, using the methods clearly understood and available today, should, in a relatively short span of years, remove pneumonia from its exalted position as third among the scourges of life in this country.

Medical science is progressing in such rapid strides, that bacterial and parasitic diseases will soon be eliminated as factors of importance which have heretofore interfered with, and too often interrupted the aging process, or the life span, of individuals. Special programs organized on a national scale, and energetically carried out by the medical profession, will go far towards controlling diseases such as syphilis and similar infections.

With the health of the people regarded as an interest of the government—Federal, State and Municipal—it is to be looked for and indeed hoped for, that in the not far distant future Departments of Health will have properly and adequately trained executives and personnel, persons educated in the broad field of public health, rather than appointees selected in a haphazard and random fashion. This move would seem necessary in any plan for adequate medical care for the nation.

### THE DEGENERATIVE DISORDERS

Once having reached middle age, the individual enters the age period when the so-called degenerative diseases, that is to say, disturbances of the heart and vascular system, high blood pressure, kidney disease, cerebral hemorrhage and diabetes appear on the horizon. These hazards of life assume an importance hitherto unconsidered because of the greater number of individuals in that age period.

The problems of middle and later life are somewhat different from those of infancy and childhood, medically speaking. They have to do more or less with the resiliency and stamina and elasticity of body tissues and organs, their hereditary background and predispositions.<sup>9</sup> The effects of the various stresses and strains of modern living conditions need to be kept in mind. Tissue resistance and repair must be studied from the chemical and physical approaches.

The wear and tear, the stresses and strains of existence need be analyzed, particularly along the lines that Bok has instituted in the study of personal problems of Harvard students. The effects of repeated acute toxic conditions, as well as low grade chronic infectious disorders, constipation and metabolic inadequacy need clarification.

With the decline in the birth rate, and at the same time an increase in the number of individuals living to mature and later years, the character of the national population is being slowly modified. The temper of the people is bound to assert itself in certain important changes which will extend into all the various phases of social, economic, political and professional life. A more mature national mind should have a steadying influence on the life of the nation.

From these observations it will readily be seen that the problem of aging is one of major dimension, and the diseases of middle and later life need to be more intensively studied than ever before.

#### METABOLIC DISORDERS AND THE AGING PROCESS

The two metabolic diseases which are most likely to interfere with the aging of the individual are obesity and diabetes. The overweight individual renders himself susceptible to a variety of disorders of the cardiovascular, gastrointestinal and other systems of the body, and in addition, is regarded as a poor risk by insurance companies. By restraint and wholesome living these individuals can add years to their life span.

Diabetes is rapidly on the increase. It has been estimated that there are more than one million diabetic patients in the United States, and that over a million more are susceptible to the disease.<sup>10</sup> Diabetes is important from the hereditary approach and as such, is a medical-social problem. Diabetics should not marry diabetics.

Investigations of the diabetic state have yielded important information regarding the process of arterial degeneration, notably one kind of arteriosclerosis. Uncontrolled diabetics, and particularly those on a high fat diet, are prone to develop hardening of the arteries early.<sup>11</sup> Likewise, they are more susceptible to coronary disease. These are problems of tissue degeneration.

*Arteriosclerosis.* Whatever the cause, sclerosis of the vascular system is certainly a form of tissue degeneration. Deposition of calcium in the injured tissues is probably a protective mechanism to safeguard the strength of the degenerated tissues. As such, it is a beneficent action of nature.

The work of T. Leary<sup>12</sup> strongly suggests metabolic deterioration as an important factor. A multiplicity of factors must be involved in the causation and, whereas the end result may be the same, a variety of influences in the nature of stresses and strains, or metabolic dysfunction, all based on a susceptible hereditary type of tissue, may explain the occurrence. No single set of experiments has been absolutely convincing. Nor is arteriosclerosis an affection of modern man, because in numerous instances sclerosis of the arterial system has been demonstrated in mummies, both of animals and man. The problem awaits solution. When the answer is found, life will certainly be further prolonged.

### NUTRITION AND LONGEVITY

Nutrition plays a part of equal, if not greater, importance than heredity in the development of a more vigorous body resistance and an extension of the span of years, according to Sherman. From experiments carried on over a long period of years on lower animals fed various types of diets, and from additional observations on human longevity, Sherman believes that, with the addition of generous portions of foods rich in calcium and vitamins A and G, six or more years of active life may be added to the prime years of human existence.<sup>13</sup> So convinced is he of this fact that he has governed his own diet accordingly. Apparently, certain factors can extend youth and increase vitality and the life span. Experimentally, it has been shown that a higher than average calcium intake is conducive to better than average health. With a calcium rich diet, there is an improvement in the utilization of food, better growth, greater adult vitality, a longer period between the attainment of maturity and the onset of senility, and, to a certain extent, an increase in the length of life. These observations were made on white rats, whose metabolism closely resembles that of the human being. The life span of man is approximately 30 times that of the albino rat, and the results are, of course, more rapidly obtained in the rat.

There is an important difference between an optimum diet and a merely adequate diet. An adequate diet, with the addition of certain important ingredients, will result in enhancement of nutritional well-being.

Sherman is of the opinion that, while the average American intake of calories is adequate, in the accepted sense, it is below that from which optimal well-being is to be expected. Foods rich in calcium such as milk, cheese, clam, eggs, vegetables, particularly beets, turnips, broccoli, cauliflower, bean, almonds and molasses, furnish a generous variety. As a problem of medical-social importance, Sherman believes that one-fifth of the food budget should be spent for milk and cream, not less than one-fifth for fresh fruit and green vegetables, and the remaining three-fifths for bread, butter, fish and eggs. Protective foods furnish propulsion power to the vital essence of existence and neutralize, at least partially, the degenerating forces within the body. By applying known facts regarding proper diet, the average life

span could be increased at least 10 per cent. Not only would years be added to life, but greater happiness, health and vigor result.

Hopkins maintains that faulty nutrition has played a large part in inhibiting human progress and he has observed that few races have been ideally nourished at any time. And according to Minot, man's place in future history will depend in no small part on diet.<sup>14</sup>

A scientifically planned diet will delay the onset of the ravages of old age. As whole milk is the ideal food for first childhood, so it can be accepted as the best single food for old age. As there is frequently a tendency towards development of a mild anemia in the later years, the use of liver twice weekly and iron rich foods will tend to maintain the level of the blood. For sluggish digestive powers and gastric atony, vitamin B<sub>1</sub> is frequently of value.

The nutritional requirements of older persons are less per kilo of body weight, but it is important that the specific foods, particularly such proteins as are contained in liver, and the vitamin B<sub>1</sub> complex and iron, be included in the diet. Likewise, a minimum fat content will protect the individuals from overweight where such a possibility exists. Much can be done with diet.

#### NORMAL AND ABNORMAL GROWTH

*A Consideration of the Nature of Cancer.* The complex problem of cellular growth needs to be clarified. In order to understand more clearly the processes of body metabolism and aging, it will be necessary to study intensively the physical-chemical balance and existence of the individual cells which, in their aggregate, make up the human organism. Orderly growth of cells gives a healthy, normal human body. Disorderly growth with cellular expansion is cancer. This disorder destroys over 130,000 individuals each year in the United States.

The fundamental issues involved in a study of normal and abnormal growth, cellular and organized, when properly understood, will furnish knowledge which will prove invaluable for the development of a more hardy and rugged human species.

Cancer is a growth; as such it should be studied. The growth characteristics of cancer are two, namely, an increase in cell number which is unusual for the site and the age, and secondly, an incompleteness in differentiation or cell maturity. Whether the immaturity is secondary to the unwonted proliferation, or the unwonted proliferation is secondary to the cellular immaturity, or whether the two distortions have separate bases is of no immediate practical importance.

What is of practical importance is the validity of the following statement, namely, "The malignant character of cancer should be diminished by retardation of its proliferation and forwarding of its differentiation activity." As Hammett has stated, the best agents to bring proliferation toward its completion, should be those which Nature itself uses for these

ends. In the naturally occurring tissue components of general distribution should be found those agents which Nature uses for the regulation of proliferation and differentiation, and hence, those natural agents which should assist in bringing cancerous growths to relative innocuity.

Proliferation of cells is regulated among other chemicals by the naturally occurring specific and essential chemical equilibrium comprised in the sulfhydryl group and its sub-oxidized derivatives. This has been used by Hammett to produce for the first time a retardation of proliferative growth in spontaneous mouse tumors in a way used by Nature to bring normal increase in cell number to its natural end.

Using comparatively simple forms of cellular life, Hammett<sup>15</sup> has shown that each naturally occurring tissue component of general distribution has its own separate and peculiar influence on growth. The further observations of Hammett and Reimann<sup>16</sup> point to the probability that growth activity is significantly favored by some pyrrole derivative, possibly the pyrrolidone configuration or some part or derivative thereof. It has been proved that differentiation is advanced in the presence of compounds which are potentially interrelated through the pyrrole grouping and in the presence of no other compounds. The pyrrole influence may be traced through such chemicals as dextro-glutamic acid, laevo-aspartic acid, laevo-tyrosine, laevo-proline, and laevo-hydroxy-proline of the amino acids, and thymine and cytosine of the nucleic acid derivatives. These chemicals have the important function of forwarding differentiation. The pyrrolidone configuration is apparently an essential substance in the completion of cell maturity. As such, its importance in the study of cancer cannot be underestimated.

If it can be found what nature uses to bring cell multiplication to an end in the natural course of events, and if it is possible to find what Nature uses to make young cells grow up, then possibly one may be able to retard cell increase in cancer and force cancer cells to mature. In this way, the tumor would no longer be a cancer and life would be prolonged.

This work just cited is highly important and suggestive. The dynamics of normal and abnormal cellular vitality must be thoroughly investigated and understood before the cause of cancer will be finally known. The coordinated efforts of investigators with assistants from various special fields as biology, physiology, physical chemistry, mathematics, statistics, etc., will solve the problem eventually.

For the carrying on of this important work public support is essential. Recently, generous funds have been made available by private philanthropies for just such work. In addition, the United States government has signified its recognition of the importance of the work. Brains are more important than buildings and funds should be utilized for the conduct of a long range plan of approach to the problem. Small grants for small-time work are not very helpful.<sup>17</sup>

Meanwhile, the public may help in the battle against cancer by keeping informed of the developments, and by health examinations at stated inter-



vals, particularly, of all individuals over the age of forty-five. Small growths or chronic sores, or warts and moles or discharges which have persisted, should be recognized and eliminated before they have developed to the cancerous state.

### REJUVENESCENCE

The hope for recapture of youthful vigor and enthusiasm, particularly in the erotic life of the individual, has been expressed by numerous observers, and has been the object of innumerable pseudoscientific investigations and treaties. Latterly, Voronoff and his followers have claimed spectacular results from testicular glandular transplants, and Steinach has advocated the severance of one or more of the glandular ducts. Extravagant claims have been made for these procedures. Numerous cases have been cited, wherein sexual power has been regained and the ability to participate in the sexual act has been described.

Such an approach to the problem of prolongation of vitality places an undeserved emphasis on the single force of sexual activity. Even were it possible to reawaken the somnolent sex life of the individual and revitalize the function and structure of the genital tract, the unwisdom of such a procedure would soon become manifest. Other vital systems, and more particularly the cardiovascular tract, central nervous system, and the muscular equipment of the body, play a more dominant rôle in the health and welfare of the elderly individual than does the genital tract. Rejuvenescence of all the tissues of the body has to date not been accomplished.

### INDUSTRY AND FORTY-PHOBIA

With more individuals attaining the middle years of life, and, at the same time, in better physical, nervous and mental condition than at any previous time, the value of their labor ability and contribution to society requires broader recognition. While physical maturity is more exuberantly evident in the early years of adult life, emotional maturity and with it, stability, comes relatively later. An individual is at his best when maturity of the physical, intellectual and emotional patterns have attained their full stature. This is probably somewhere between the years of forty and sixty. Therefore, it should be realized that persons from forty on, most likely bring to their work the factors that make them most useful. Mature individuals in the middle years are less restless, have a better appreciation of values, have more experience, have an understanding of proportion impossible in youthful adults, and are likely to be more valuably productive.

A recent survey of some of the country's largest industries, which report was made to the Sales Executive Club in New York, indicated that individuals over forty are more conscientious than those under forty, that they are more open-minded toward criticism, that they undertake unpleasant tasks more willingly, and finally, bring in more new ideas of value.

The attributes credited to young men such as enthusiasm and cheerfulness, prompt adaptability, more attention to personal appearance, and promptitude in developing a new assignment are equally applicable or possible to individuals of more mature age.

A recent study of 1,444 skilled workers on WPA projects,<sup>18</sup> showed that those receiving higher grades for quality of work were also in the higher age brackets. The average age of those workers graded as excellent was 47 years and the average of those counted inferior was 41 years. The survey further indicated that older men produce more than younger men at any set task. It is encouraging to note that the average age of automobile workers is rising and in more and more divisions the tendency is to give preference to men over forty, particularly for the handling of multiple machines.

In a challenging article recently, Waldemar Kaempffert has discussed "The Man Over Forty: A Machine Age Dilemma."<sup>19</sup> Kaempffert cites four charges that industry has made against the man over forty.

First, that he is a bad physical risk. It is said that, over forty, a man enters the period of life when the degenerative diseases will lower his efficiency or incapacitate him entirely. Certainly, there is a relation between occupation and health and longevity, which industry does not take into account. The highest death rate occurs among the unskilled and semi-skilled callings. When individuals falling in these occupation groups are favored with the benefits that modern science has to offer toward a more vigorous and prolonged existence, and when industry improves the conditions under which such laborers carry on, it will be found that the death rate can be substantially reduced. The man over forty is not of necessity a bad physical risk.

The second charge is that of lowered productivity; but recent measurements, as pointed out, have indicated that the period of greatest productivity may lie somewhere between 47 and 60 years, so that this charge can be substantially refuted today. There is strong physiological and psychological evidence that many men are just as proficient at 50 or 60, or even more so, than their younger competitors. As the benefits of science in the form of nutrition and a more intelligent, personal hygiene are extended to large groups of workers, and conditions under which they labor are improved, their productivity will certainly increase.

Third, it is said that individuals above 40 years of age are bad accident risks. But here, as Kaempffert has emphasized, this attitude of industry is definitely in error. To prove his point, he cites a survey which differentiated between jobs held by the young and the old, as studied by the British Industrial Health Research Board. This Board found that the man over 40 was more careful and conscientious than his younger competitor. Age and experience have definite dividends to offer. The British findings are likewise confirmed in a study of 65 manufacturing plants and four railroad repair shops in the state of New York.

The fourth charge is that men above 40 are too slow and unadaptable to

changing conditions. Then again, the same statement concerning the benefits of improved personal hygiene and scientific nutrition and better working hours and better working conditions, will tend to make the man over 40 practically as adaptable as the one under forty.

In a day when overproduction is the rule, high pressure methods whereby still more goods may be produced or manufactured are definitely unnecessary. American industry has too frequently driven its masses of men at a feverish pace, to their detriment. A marked deceleration of this pace would contribute immeasurably to the nation's peace of mind and health of body.

At the present time, 260 out of every 1,000 persons living in the United States are 40 years or over in age. By 1960, statisticians estimate that 36 per cent of the population will be between the ages of 40 to 65 years. With more and more able bodied individuals at mature age levels, the need for new industries together with a more profitable use of leisure carry new meaning.

### THE RETIREMENT PROBLEM

The practice of retiring individuals after a certain age limit has been reached, is widespread in business, industry and the professions. Labor organizations have long been in favor of the retirement age, at which time a worker is placed on pension. One of the major benefits derived from this principle is the creation of enlarging opportunities for younger men on their way up, by the creation of openings in positions of responsibility.

With the increasing span of useful life, particularly in lengthening of the productive years, large numbers of individuals, both men and women, will be displaced at a period in their lives when their individual productivity has not been diminished. And in those individuals whose physical stamina is lessened, there yet remains the important factor of experience which is always an asset. This is a problem of growing importance today.

The resourceful individual always has a multiplicity of interests and enthusiasm that challenge his energy and time allotment. Retirement for this individual means but the transference of interest from one activity to another.

It is difficult to designate a year age at which time those engaged in any specific work should be relieved of further responsibility, since the vitality and ability to carry on is an entirely personal matter.<sup>20</sup> With a clearer appreciation of scientific nutrition and improved methods under which man labors, his period of productive maturity should extend into the later years of life. Furthermore, it has been generally recognized that individuals possess a generous physical and nervous reserve which is rarely utilized.

Retirement too often for the individual means rust as well as rest. The profitable use of leisure determines the fullness and value of the later years, particularly of that period subsequent to retirement.

## SOCIAL IMPLICATIONS OF LONGER LIFE

With more effective control of life-destroying degenerations, malignancies, infections, deficiencies and traumas, the life span of man is going to be lengthened and the mature and productive years will be more in number and, it is to be hoped, the senile period will be reduced to a shorter time.

Labor-saving devices together with improved conditions and sanitation for workers, and more hours of leisure for the laboring class, help to preserve the vital essence of the living process and prevent the body from aging faster than the mind.

As living conditions and the various details of human existence improve more persons reach old age and, therefore, their futures need be reckoned with. Today, little, if anything, is done to fit individuals for old age, and they reach it unprepared and uninformed. The dearth of knowledge concerning the needs of the aged has been repeatedly emphasized by Carrel,<sup>21</sup> Sherman, Pearl and others. An intelligent and well-conserved senectitude has important social and anthropological functions.

Hall<sup>22</sup> points out that present day society is characterized by distracting specializations of work and interests. The synthesis of social existence, that is, the unification of the various integrated streams of human interest, can best be accomplished by mature individuals with adequate years of experience and an appreciation of life as a whole.

New problems of medical-social value loom in the foreground. The conquest of the unknown has gone forward at an incredible rate. New methods and disciplines are being developed. Cannon has pointed out that the hardest tasks confronting the medical profession are those related to the nature of man and the factors which determine his conduct.<sup>23</sup> It is the inhumanity of human beings that spoils the achievements of science. As major disorders of the intellect and personality are now under scientific scrutiny and not infrequently responding to beneficent treatment, other inhuman traits such as cruelty and belligerency may be considered within the realm of medical accessibility.

Cannon asks, "What can be done to improve human behavior?" And he states, "Here, one confronts the most important frontier of all." The problem of human motivation becomes a medical-social challenge. Cannon points out that potent biological factors which shape the ends of men are now known that have heretofore never been dreamed of. And recently, investigators using methods which proved effective in the past have begun to unravel and evaluate the strength of some of the forces which play an important rôle in determining what man is and what activates him.

The cretinous idiot can be transformed into a child with normal intelligence. The patient with schizophrenia but recently has responded to treatment. The powerful forces which shape man and his destiny and which exist within him are now being subjected to the intensest kind of scientific analysis. A great and as yet uncharted realm of profound medical and social significance awaits exploration.

The revolution which is reshaping medical science is not merely a fight against death, but also, a fight for life with all the implications, both economic and social, which emerge from science's successful lengthening of the life span, as Gray has so ably described.<sup>24</sup> The society which fosters research to save human life cannot escape responsibility for the life thus extended. It is for science not only to add years to life, but more important, to add life to the years.

In the words of Charles E. Merriam, "If the devices of social invention are able to keep pace with the scientific organization of nature, the new road may lead to a fairyland of achievement."<sup>25</sup> The burdens of hunger, disease, toil and fear may be listed. Leisure and the treasures of human appreciation and enjoyment may be available to all mankind. The diseases of intolerance and the lust to kill may respond to treatment just as some of the other mental diseases heretofore regarded as incurable.

What group of society is qualified by training, experience, and broad interest to investigate these problems of vital importance to the world today if it is not the medical profession? Industry, government and church have their varied and justifiable interests in other aspects of the individual. The medical profession alone studies him from the somatic, nervous, intellectual, and emotional approaches, learns his assets and his liabilities and endeavors to help him to take his position in the social plan.

An intensive consideration of the aging process is bound to lead to worthwhile data. From the facts thus obtained, individual existence should be enriched, which, after all, is about as good an objective as any towards which the medical profession can direct its interests.

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# A CLINICAL STUDY OF MALIGNANT HYPERTENSION \*

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PHYSICIANS have long recognized that the clinical course of arterial hypertension is exceptionally variable. The lives of some patients appear to be little shortened by elevated blood pressure while others succumb within periods measurable in months. Volhard and Fahr (1914) emphasized these differences by the terms "benign" and "malignant," and Volhard pointed out that the benign form of hypertension may at any time turn malignant.

For some years the genesis of hypertension which showed signs of a rapidly fatal outcome was ascribed to the kidneys. Scant regard was paid the blood vessels in the remainder of the body. The morbid state was variously called "malignant nephrosclerosis" or "genuine contracted kidney." Fahr (1919), Volhard (1918), Fishberg and Oppenheimer (1930), and Wagener (1930) later demonstrated that the lesions were not limited to the kidneys and that retinal change is the earliest observable sign.

Keith, Wagener, and Kernohan (1928) presented a classic description of 81 patients of arterial hypertension with characteristic retinitis, adequate renal function, and rapidly fatal outcome. Less importance was attached by them to the part played by the kidneys in the genesis of the syndrome. The ubiquity of the arterial damage was stressed. They termed this type of hypertension the "syndrome of malignant hypertension." These observations were shortly confirmed and extended by very careful studies of Murphy and Grill (1930). Ellis (1932) has published one example of each of four clinical types of malignant hypertension—cerebral, cardiac, renal, and combined. Observations on the clinical course of malignant hypertension which agree closely with those in this paper have just appeared from the pen of Arthur Ellis (1938).

The origin of the syndrome of malignant hypertension is obscure. Volhard, in particular, believes that the kidneys participate in its genesis. Its occurrence, superimposed on essential hypertension, suggests that it might be the result of acceleration of the mechanism responsible for the latter. This theory is as yet without objective support. Derow and Altschule (1935) believe it to be of multiple etiology.

Klemperer and Otani (1931) have ably summarized the literature concerning "malignant nephrosclerosis." Suffice it to say here that the clinical signs and symptoms of malignant hypertension may occur both with and without evidence of severe renal damage as determined by contemporary laboratory methods. But this does not prove that the kidneys are not involved in the genesis of the clinical syndrome of malignant hypertension.

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A disease closely resembling malignant hypertension has been produced in dogs by tight clamping of the main renal arteries by Goldblatt (1938). Renal insufficiency appeared to be an essential factor in its development. Necrotic arterioles and hemorrhages were not observed in animals that had very high blood pressures for years without renal insufficiency, nor in animals with azotemia due to removal of both kidneys, but without hypertension. Ischemia was not the cause of the arteriolar necrosis because it was absent in dogs' kidneys made ischemic and widespread in other organs that were not ischemic. The necrotic arterioles and hemorrhages were secondary to and not the primary cause of this type of malignant hypertension.

The author can confirm Goldblatt's observation, for five examples of malignant hypertension have been observed which correspond in most details to his convincing description of the syndrome. Especially impressive were the changes in the eyegrounds which consisted of intense arteriolar constriction, arteriovenous compression, sclerosis, hemorrhage, exudate, papilledema, detachment of the retina, and blindness, just as observed by Keyes and Goldblatt (1937).

Most clinicians agree that malignant hypertension may be engrafted upon essential hypertension. Such cases are common and will be omitted from the records of patients presented in this communication. Hypertension appears to have been malignant from the onset in our 30 patients. Since these patients were followed in the Hospital of the Rockefeller Institute at intervals for periods up to seven years, it was believed of interest to present pertinent observations from their records.

### METHODS

Renal efficiency was measured by urea clearance and ability of the kidneys to concentrate urine. Urea clearance was employed not only because it is a most delicate test but because Van Slyke, Rhoads, Heller and Alving (1934) have shown that in dogs it parallels the renal blood flow. The specific gravity was measured of a twelve-hour specimen voided at the end of 24 hours without fluids. If protein was present in sufficient amount to contribute to the specific gravity, a correction was made for it; that is, 0.003 was subtracted from the total specific gravity for each 1 per cent of protein. The number of formed elements in the urine was estimated by the technic of Addis (1926). Not more than 500,000 red blood cells are excreted by a person with normal kidneys. The protein content of the urine was measured by the method of Shevky and Stafford, as slightly modified by McKay (1932). The protein content of the plasma was ascertained by the method of Howe (1921), and the hemoglobin content was measured by the Van Slyke and Neill oxygen capacity method (1924).

*Explanation of the Charts.* On the charts the mean normal of each measurement represented is drawn as a base line; the shaded areas between the base line and the points representing observations indicate the degree of deviation above or below the average normal. The brackets at the left of



the scales for urea clearance, concentration of urine, and hematuria indicate the range of normal variability. The normal base line for the hemoglobin value varies with the patient's age and sex. Measurements of the blood pressure were made daily at 9:30 A.M., *but are represented in the charts as averages.* Morbid changes in the eyegrounds are recorded as follows: (1) constriction of the arterioles, (2) arteriosclerosis, (3) exudate, (4) hemorrhages and (5) papilledema. The estimated time which elapsed between the onset of the disease and the patient's admission to the hospital is recorded on the lowest line of the chart as the first number following the word "months." The other numbers in the bottom row indicate months after patient's first admission to the hospital.

### RESULTS OF STUDY OF PATIENTS

Thirty patients were studied (table 1). Nineteen of these were males and 11 females, varying in age from 14 to 48 years (average 33 years). Of these, 24 are dead, 5 alive and 1 patient was not followed. Six patients were subjected to the operation of anterior spinal nerve root section and have been described in a previous communication (Page and Heuer, 1937). Three of these (Nos. 2, 13, 18) are alive and 3 dead (Nos. 4, 5, 12). Supradiaphragmatic splanchnic nerve section was performed on three patients (Nos. 1, 3, 30) and all are dead (see Page and Heuer, 1937).

The chief complaints in order of their frequency were headache (13 patients), visual disturbance (7 patients), fatigue (4 patients), dyspnea (2 patients), convulsions (1 patient), fainting (1 patient), weakness (1 patient), precordial discomfort (1 patient), and edema of ankles (1 patient). One-third of the patients stated that high blood pressure occurred in their families, but in only five was this definite enough to suggest that it may have had a bearing on the patient's illness. It is of interest that seven patients had had scarlet fever and one chorea. The past history of the remainder did not appear significant.

Since the high-strung, neurotic temperament is commonly observed in patients suffering from essential hypertension, it was considered of interest to observe whether similar primitive emotional behavior was present in those with the syndrome of malignant hypertension. Twenty of the 30 patients were classified as being emotionally unstable, but only 11 were definitely so. Few of them exhibited signs such as blushing and crying, part of the "hypertensive diencephalic syndrome" (so-called because of its resemblance to the signs and symptoms which follow stimulation of centers in the diencephalon (Page, 1935)), which may often be associated with cases of essential hypertension.

The feeling of fatigue was very common, occurring in all but nine patients. In spite of this, it was the chief complaint in only four of them. Except for dyspnea on exertion, which occurred in 21 patients, other signs or symptoms referable to the heart were rare. "Cardiac" pain was experienced in five patients and palpitations in twelve. Palpitations were

TABLE I  
Incidence of Signs and Symptoms in 30 Cases of Malignant Hypertension

Case No.	Sex	Age	Duration of Disease from Onset to Death (in Months)	Chief Complaint	Family History	Past History	Temperature	Fatigue
1	M.	48	9	Weakness	0	Scarlet Fr. 2 yrs.	++	++
2	M.	44	Alive (Ant. root sec.)	Weakness and failing vision	++	0	++	0
3	M.	18	29 (Splanchnic sec.)	Headache	0	0	0	0
4	F.	43	18 (Ant. root sec.)	Blurred vision	++	Scarlet Fr. 18 yrs.	++	++
5	M.	26	14 (Ant. root sec.)	Blindness rt. eye	0	0	0	++
6	M.	14	25	Convulsions	0	0	0	++
7	M.	40	28	Headache	0	0	0	0
8	M.	25	71	Headache	0	0	0	++
9	M.	46	Alive	Dyspnea	++	Scarlet Fr. 8 yrs.	++	++
10	M.	37	58	Headache	0	Scarlet Fr. 29 yrs.	++	++
11	M.	24	48 (Ant. root sec.)	Fainting	0	0	0	0
12	M.	37	48 (Ant. root sec.)	Headache	0	0	0	0
13	M.	24	Alive (Ant. root sec.)	Blurred vision	0	0	0	0
14	F.	36	78	Blindness	0	0	++	++
15	F.	21	19	Fatigue	0	Scarlet Fr. 7 yrs.	++	++
16	M.	25	81 (Splanchnic sec.)	Headache	0	0	++	++
17	F.	45	—	Blindness	0	0	++	++
18	F.	21	Alive (Ant. root sec.)	Headache	0	Scarlet Fr. 10 yrs.	0	++
19	F.	39	19	Dyspnea	0	0	++	++
20	M.	48	20	Precordial discomfort	0	0	++	++
21	F.	34	48	Headache	0	Scarlet Fr. 8 yrs.	0	++
22	F.	37	48	Headache	++	0	++	++
23	M.	48	48	Headache	0	0	++	++
24	F.	33	About 4 years	Fatigability	0	0	++	++
25	F.	33	54	Edema of ankles	++	0	++	++
26	F.	24	37	Failing vision	++	0	++	++
27	M.	40	64	Fatigability	0	0	0	0
28	F.	26	53	Headache	0	0	++	++
29	F.	21	Alive	Blurred vision	++	Chorea 10 yrs.	++	++
30	M.	40	129	Headache and fatigue	++	0	++	++



severe in three patients and caused them annoyance. The genito-urinary system also produced few symptoms. Nocturia occurred in 19 patients, but was troublesome in eight.

Nausea and vomiting were complained of by one-third of the patients. They were severe in only one. Weight loss, which was noted in 17 of the patients, was moderate in 15, and severe in 2.

The chief cause of death was difficult to ascertain in many of the patients because of concomitant failure of more than one organ. Uremia was believed to be the chief cause in ten patients, cardiac failure in seven, and apoplexy in four.

The results of laboratory examinations as well as certain pertinent data from physical examinations are given for most of the patients in the graphic charts. This enables one to follow the course of the disease without recourse to the many figures involved.

Renal function was measured by urea clearance and maximal ability to concentrate urine when the patient was admitted to the Rockefeller Hospital. Urea clearance was above 55 per cent of normal in 60 per cent of the patients, between 20 to 55 per cent in 27 per cent, and below 20 per cent in 13 per cent of the cases. The average time which had elapsed before the urea clearance was performed in the three groups was 31, 25, and 36 months after the estimated onset of the disease.

The maximal ability to concentrate urine was found between the normal limits of 1.024 to 1.031 in 21 per cent of the patients. It was reduced, i.e., 1.014 to 1.024, in 50 per cent and sharply reduced or lost, i.e., 1.008 to 1.014, in 29 per cent of the cases.

The hemoglobin as estimated by oxygen combining capacity and expressed in volumes per cent was found slightly above normal (21 to 23 volume per cent) in 14 per cent of the patients, normal (18 to 21 volume per cent) in 50 per cent, below normal (14 to 18 volume per cent) in 30 per cent, and sharply reduced (11 to 14 volume per cent) in 6 per cent. Plasma proteins were normal (6.8 to 7.8 gm. per 100 c.c.) in 58 per cent of the patients, slightly reduced (6.0 to 6.8) in 32 per cent and moderately reduced (5.4 to 6.0) in 10 per cent.

Morbid changes in the composition of the urine were for the most part slight. One-half (53 per cent) of the patients excreted less than a gram of protein in 12 hours, while 40 per cent excreted from 1 to 5 grams. The urine of only 7 per cent of the patients contained more than 5 grams of protein. The number of red blood cells in the urine was within normal limits in 64 per cent of the patients, exceeding these limits (from 1 to 5 million cells in 12 hours) in 16 per cent. Marked hematuria (5 to 20 million cells) occurred in 20 per cent.

Teleradiograms were made of the patients' hearts on admission to the hospital. The transverse diameter of the cardiac shadow was measured and compared with the internal diameter of the chest. The ratio,  $\frac{\text{diameter of heart}}{\text{diameter of chest}}$ , was below 55 per cent in 40 per cent of the cases (table 2).

TABLE II  
Electrocardiographic and Roentgen-Ray Findings in Malignant Hypertension

Case No.	Electrocardiogram *			X-ray			Of Skull	
	T-waves Leads		A-V conduction time in seconds	Left axis deviation	Other changes	Of Heart		Diam. heart Diam. chest
	I	II				Total transverse diameter in cm.	Total internal chest diameter	
1	+	+	0.24	lad	R <sub>1,2,3</sub> split	13.2	29.0	46
2	+	+	0.16	lad	P <sub>3</sub> diphasic	10.2	23.5	44
3	+	+	0.10	lad	P <sub>2</sub> high	16.8	28.0	60
4	+	+	0.17	lad		17.2	27.4	62
5	+	+	0.20	lad		11.0	23.5	47
6								
7			0.14	lad				
8			0.14	lad		13.8	24.5	56
9			0.17	lad	R <sub>1,2,3</sub> split, Q <sub>3</sub>			
10			0.16	lad	Q <sub>3</sub>	13.8	26.0	53
11			0.15	lad	-P <sub>3</sub>	15.5	32.0	49
12			0.14	lad	QRS <sub>2,3</sub> split	13.2	27.7	48
13			0.17	lad	Q <sub>3</sub>	13.1	26	50
14			0.17	lad	P <sub>2</sub> split	11.8	23.7	49
15			0.14		R <sub>1,3</sub> split	14.4	21.2	68
16			0.19			14.6	26.8	54
17						13.7	23.0	59
18			0.12	lad	-P <sub>3</sub>	14.5	26.4	55
19			0.14	lad		14.6	25.6	57
20			0.19	lad		17.7	29.5	60
21							walls thinned	
22			0.12	lad	P <sub>2</sub> split	14.5	26.0	56
23			0.16	lad		18.1	28.8	63
24			0.16	lad		15.5	23.5	66
25			0.18	lad		19.7	23.9	82
26			0.16	lad		14.8	28.0	53
27			0.16		Q <sub>2</sub> R <sub>3</sub> split	17.6	31.5	56
28			0.17	lad				
29			0.13		P <sub>3</sub> diphasic	13.5	23.4	57
30			0.18	lad		13.8	24.5	56

\* These electrocardiograms were taken by Miss M. Allecman through the courtesy of Dr. Alfred Cohn.

The remainder were above. In most patients enlargement of the heart was moderate. However, as the disease advanced enlargement was often, though not always, very rapid.

The electrocardiographic deviations from normal were often marked (table 2). Negative T-waves were observed in Lead I in 56 per cent of the patients, in Lead II in 50 per cent, and in Lead III in 25 per cent of the patients. The T-waves were isoelectric in Lead I in 14 per cent of the patients, in Lead II in 10 per cent of them, and in Lead III in 7 per cent of the patients. Preponderance of the left ventricle was noted in the majority (82 per cent) of patients. Other changes such as splitting of the QRS complex and negativity of the P-waves were only occasionally observed. The P-R interval was greater than normal (normal = 0.20 second) in only one patient (No. 1).

Stereo-roentgen photographs were made of the skulls of the patients (table 2). The only unusual finding was the frequent occurrence of calcification of the pineal gland. This was observed in 55 per cent of the cases. Ten per cent showed changes from normal in the sella, but they were not of sufficient grade to be considered significant. At autopsy of one of these patients nothing abnormal was found in the sella.

Examination of the ocular fundi showed extensive morbid changes in all patients. Particularly impressive was the intense constriction and tortuosity of the arterioles. In the eyegrounds of some of the patients the number of vessels appeared to have decreased markedly, only a few irregular ones remaining. In some the vessels were straightened. Arterio-venous compression was usual. The veins appeared large in comparison to the size of the arterioles, of abnormally dark color, and tortuous. Edema and detachment of the retina were common. Papilledema of marked degree was present in many cases. Exudate as well as hemorrhages were observed in all cases. In all but three of the patients who were not operated upon, these pathological signs became more extensive as death approached. These three, subjected to the operation of anterior nerve root section, exhibited marked regression of the fundus changes (Cases 2, 13, 18). This consisted of disappearance of hemorrhages, exudate, and papilledema in two cases (13, 18) and marked regression in the third (2). In seven of the patients partial or complete blindness occurred. Secondary glaucoma was observed in one patient. The tension in one eye was so great that it could not be registered by a Schiötz tonometer. After anterior nerve root section, the tension returned to normal (Case 18).

Nothing characteristic was observed about the blood pressure except its elevation. The systolic pressure was usually very high (230 to 260 mm. Hg), but by no means always (see Case 5). The diastolic pressure was rarely below 140 mm. Hg and the pulse pressure tended to be somewhat reduced (see Case 25 for example). The diastolic pressure rarely exhibited a tendency to fall (see Case 20) except during the terminal phase when cardiac failure supervened.

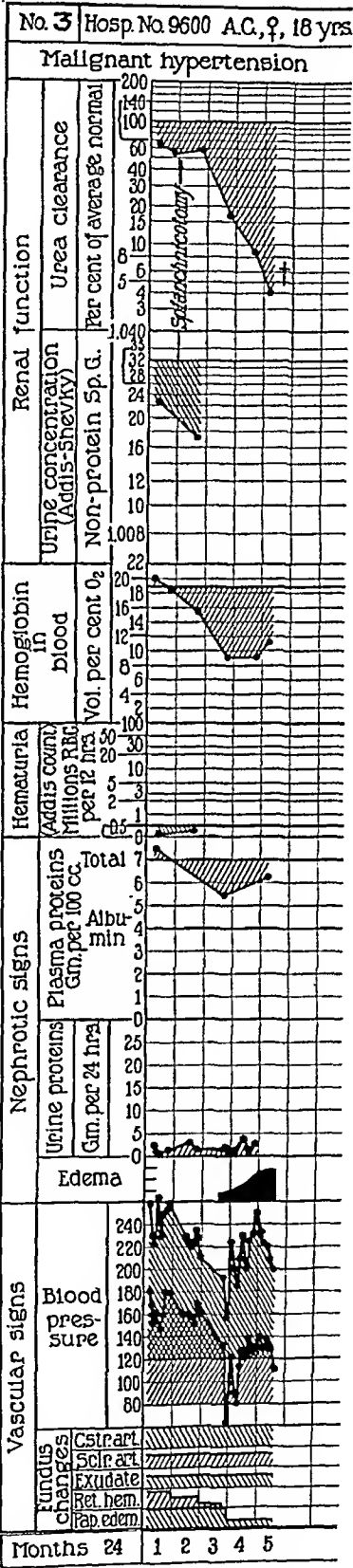
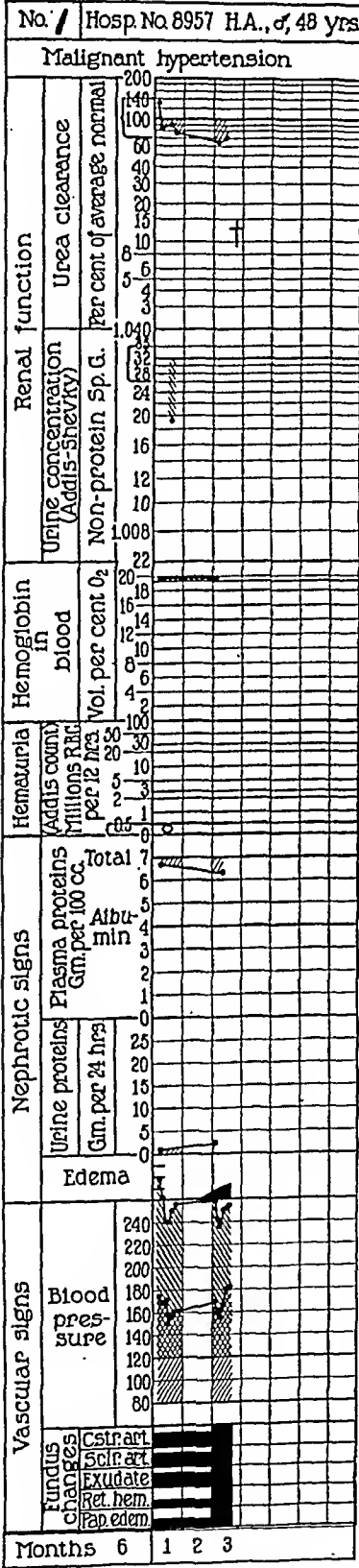


FIG. 1. Clinical and laboratory data depicting the course of malignant hypertension. Cases 1 and 3.

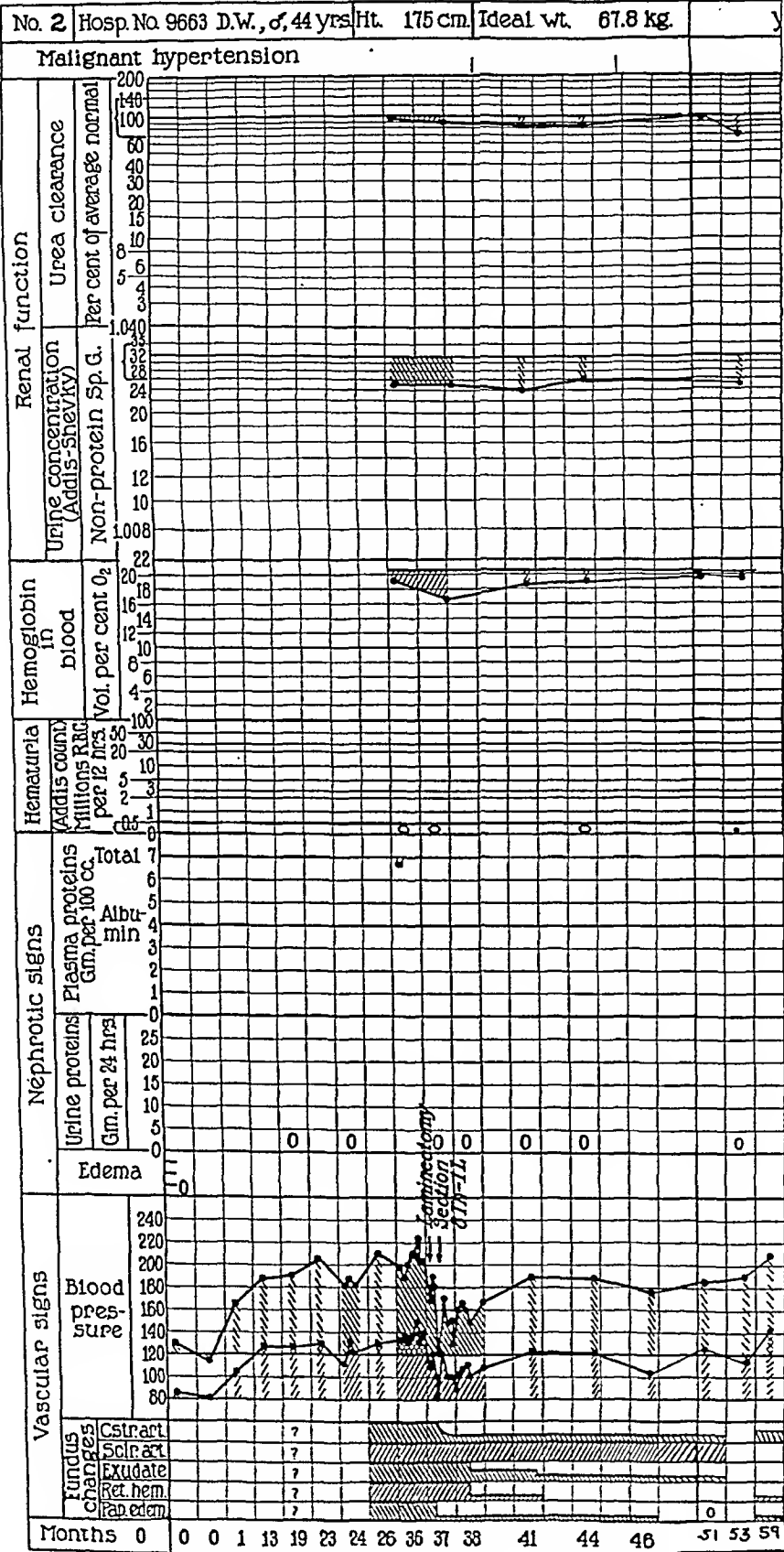


FIG. 2. Clinical and laboratory data depicting the course of malignant hypertension. Case 2.





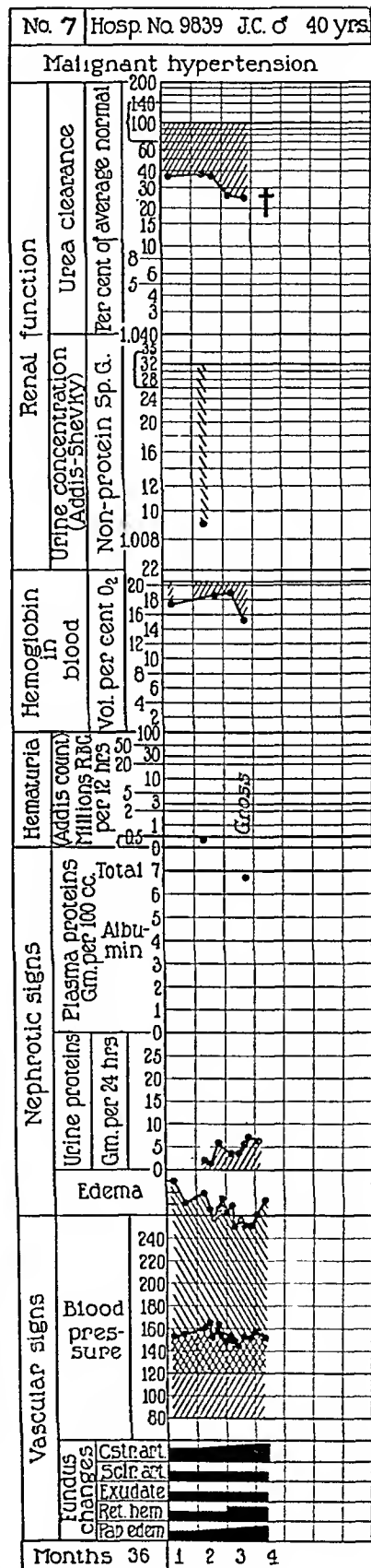
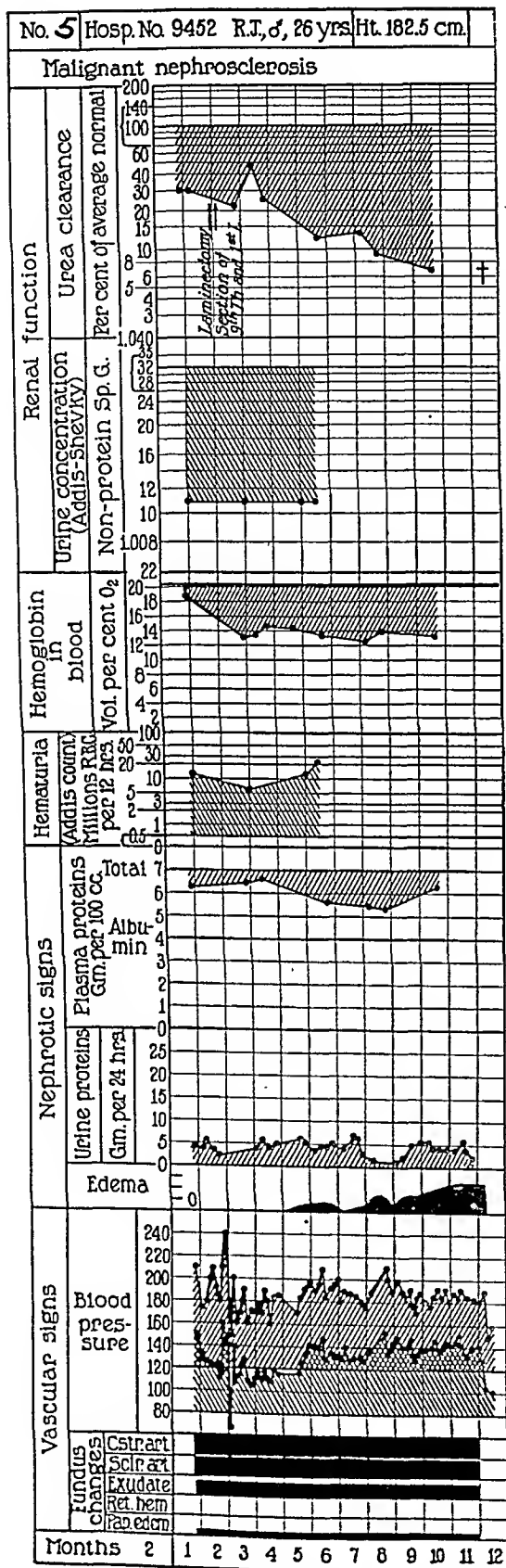


FIG. 4. Clinical and laboratory data depicting the course of malignant hypertension. Cases 5 and 7.

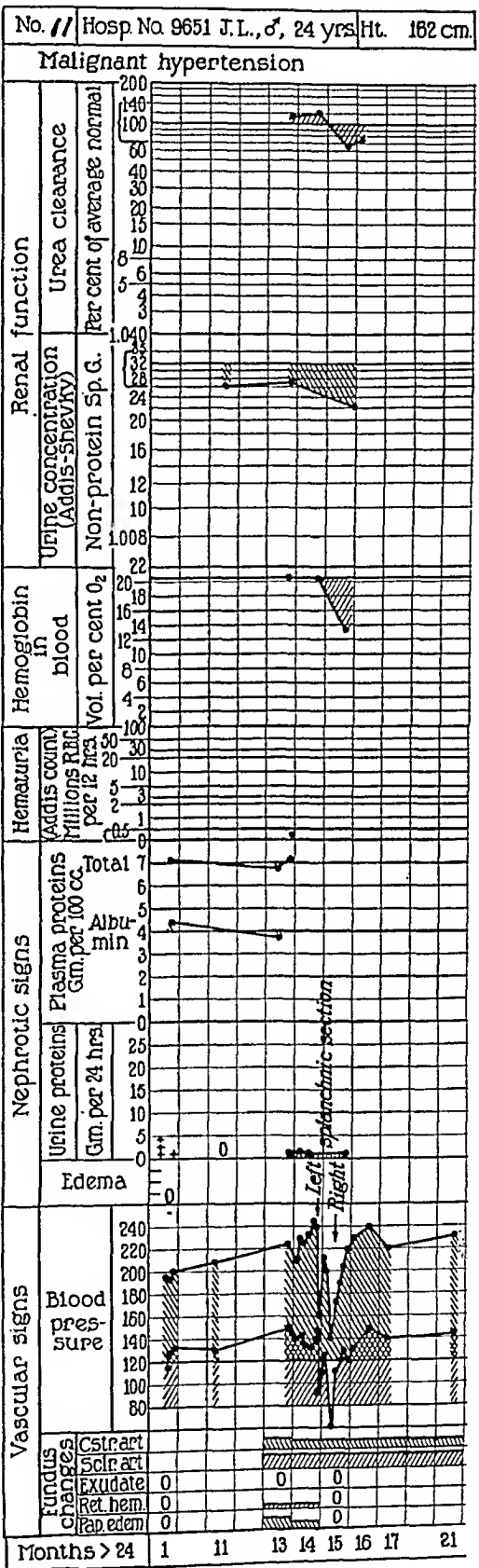
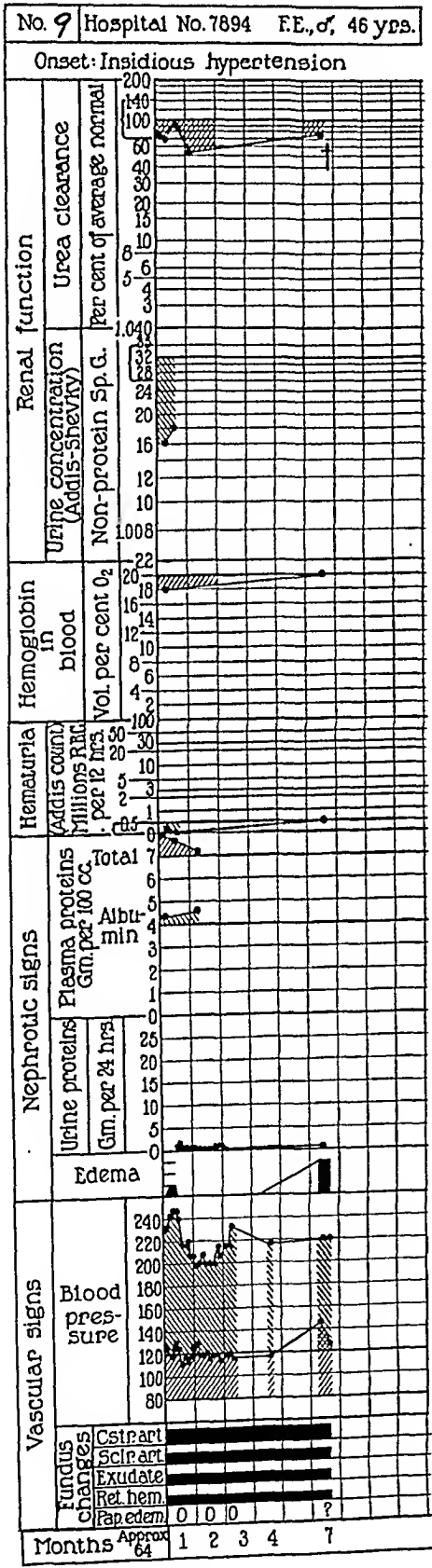


FIG. 5. Clinical and laboratory data depicting the course of malignant hypertension. Cases 9 and 11.

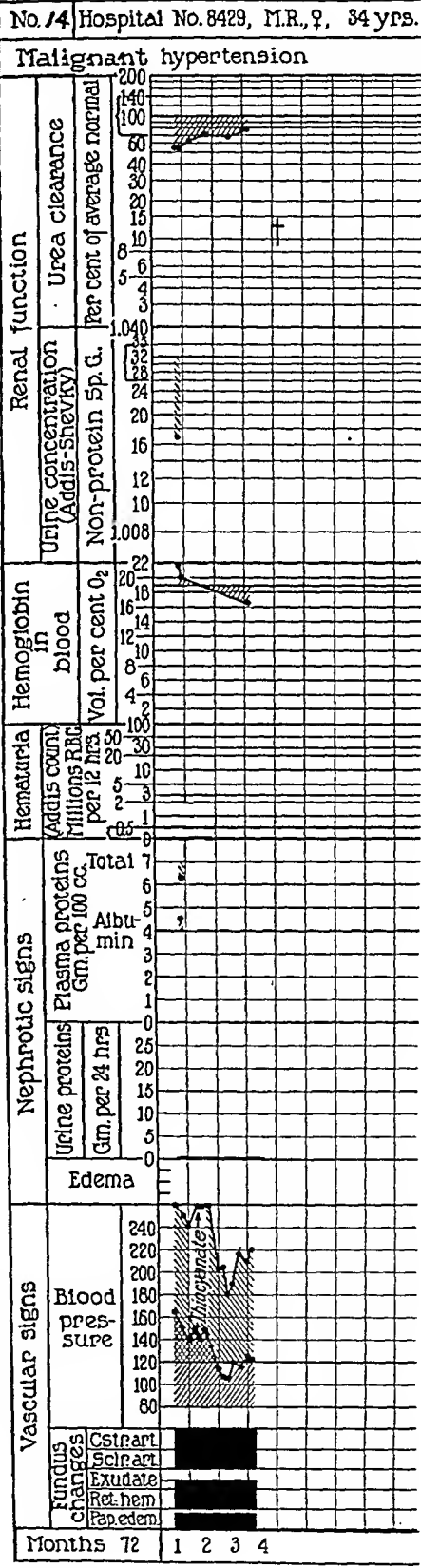
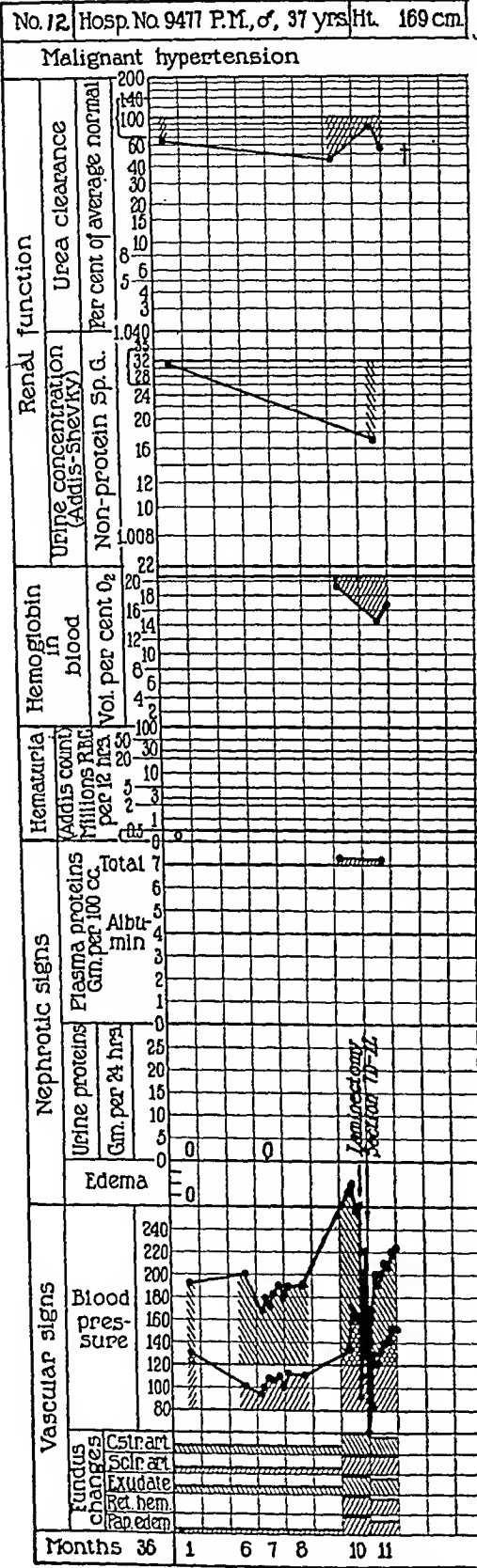
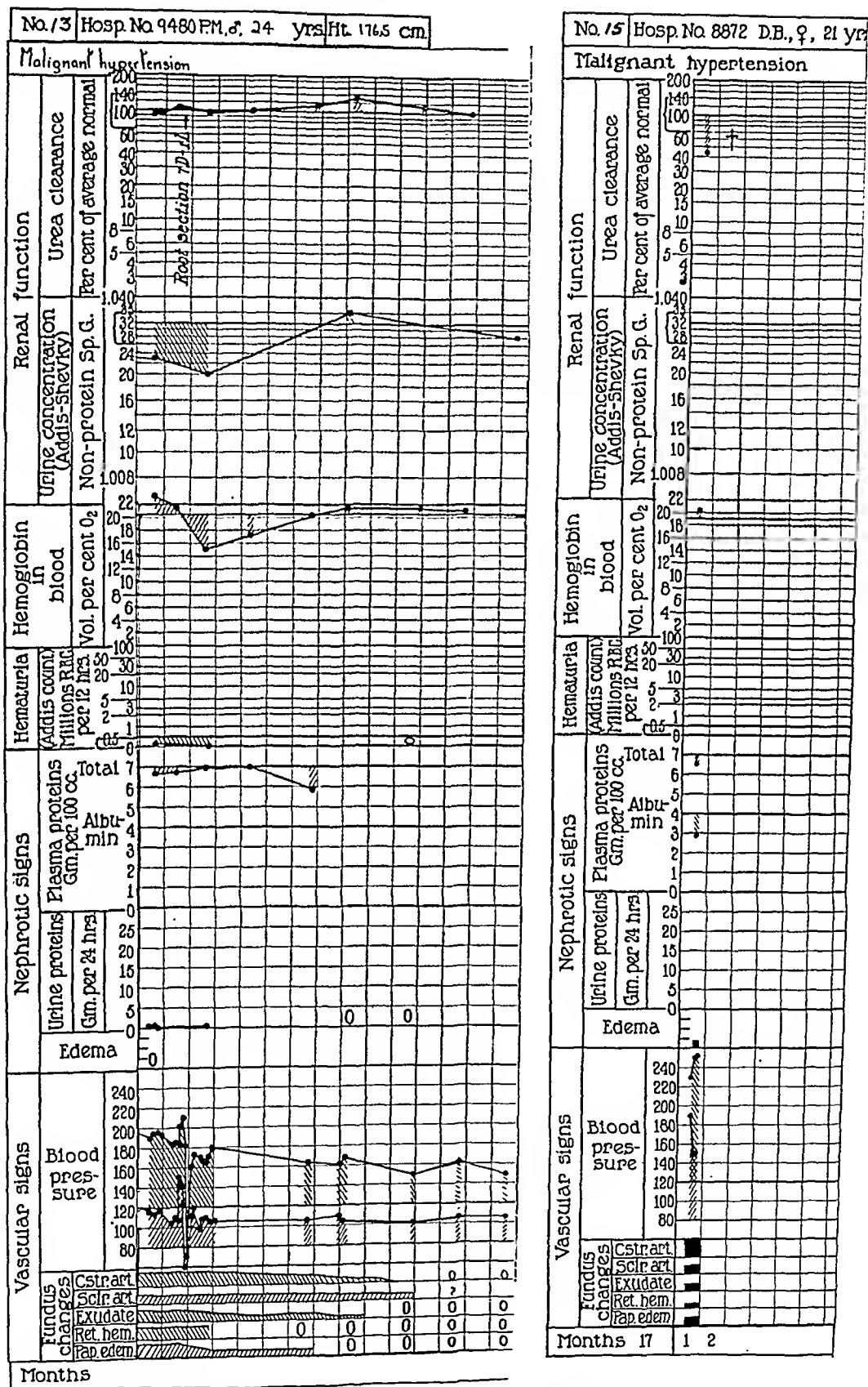


FIG. 6. Clinical and laboratory data depicting the course of malignant hypertension. Cases 12 and 14.



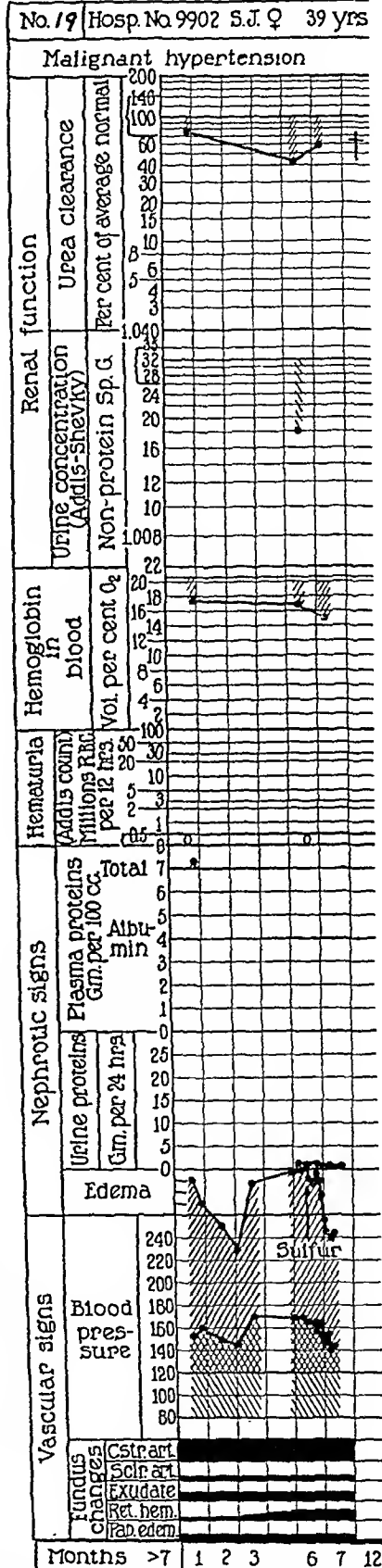
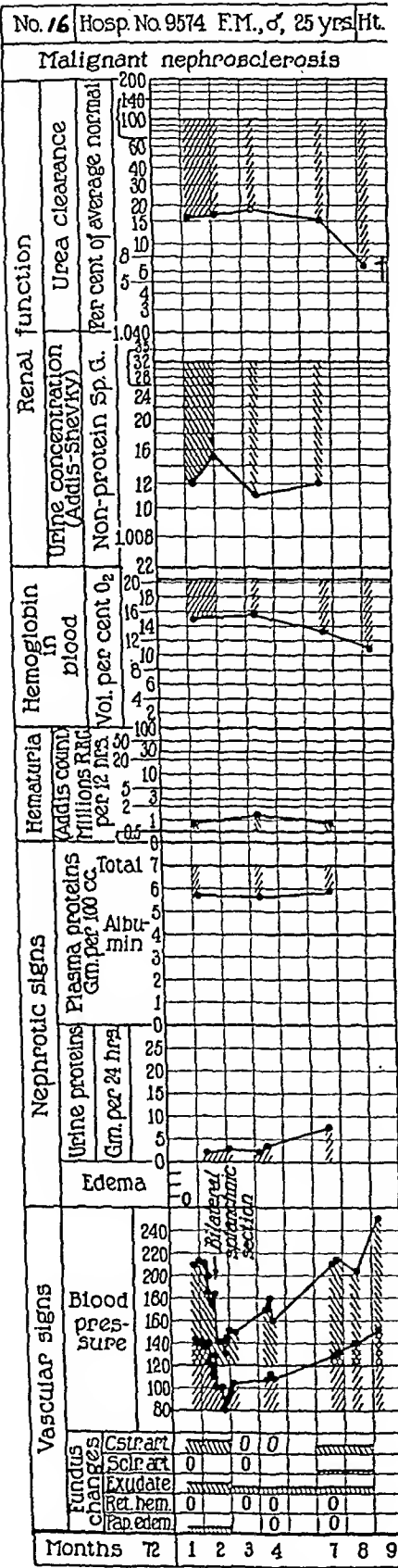


FIG. 8. Clinical and laboratory data depicting the course of malignant hypertension. Cases 16 and 19.

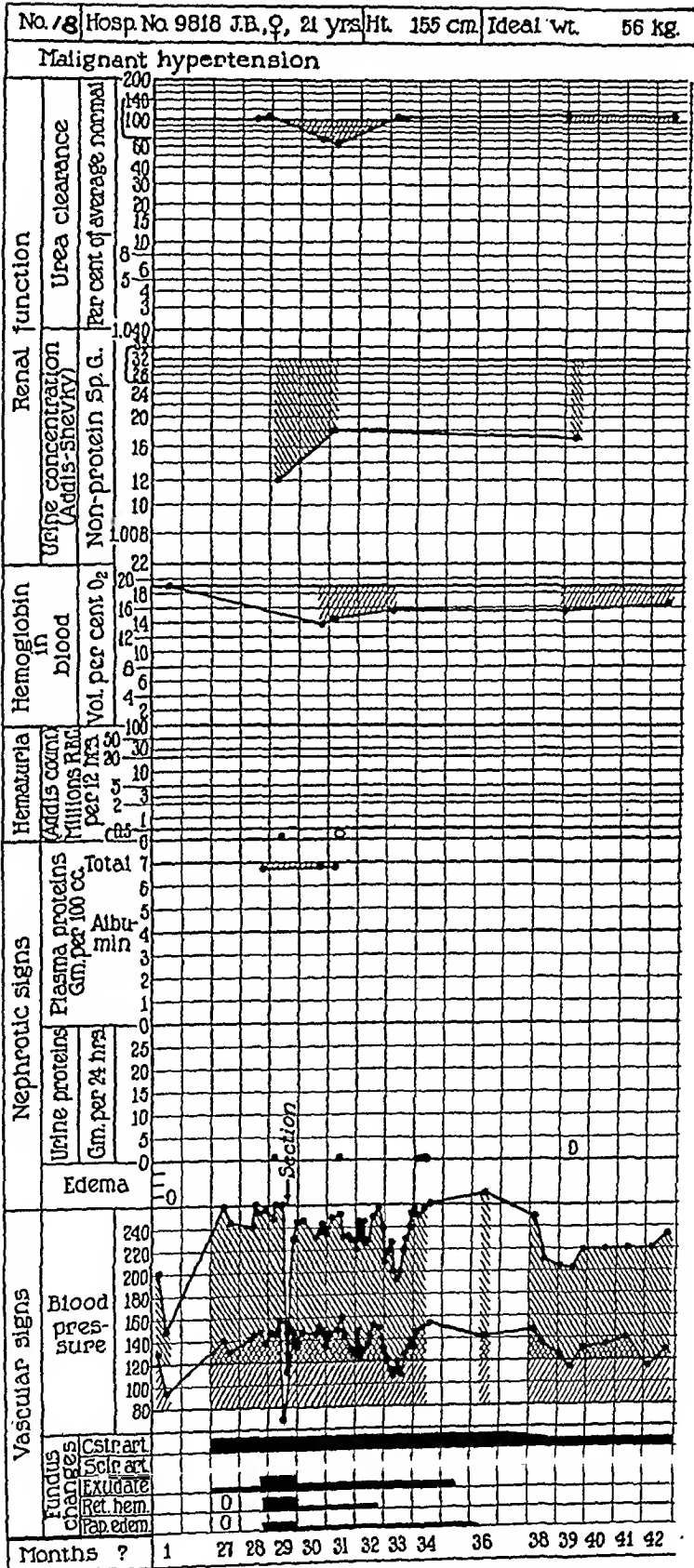


FIG. 9. Clinical and laboratory data depicting the course of malignant hypertension. Case 18.

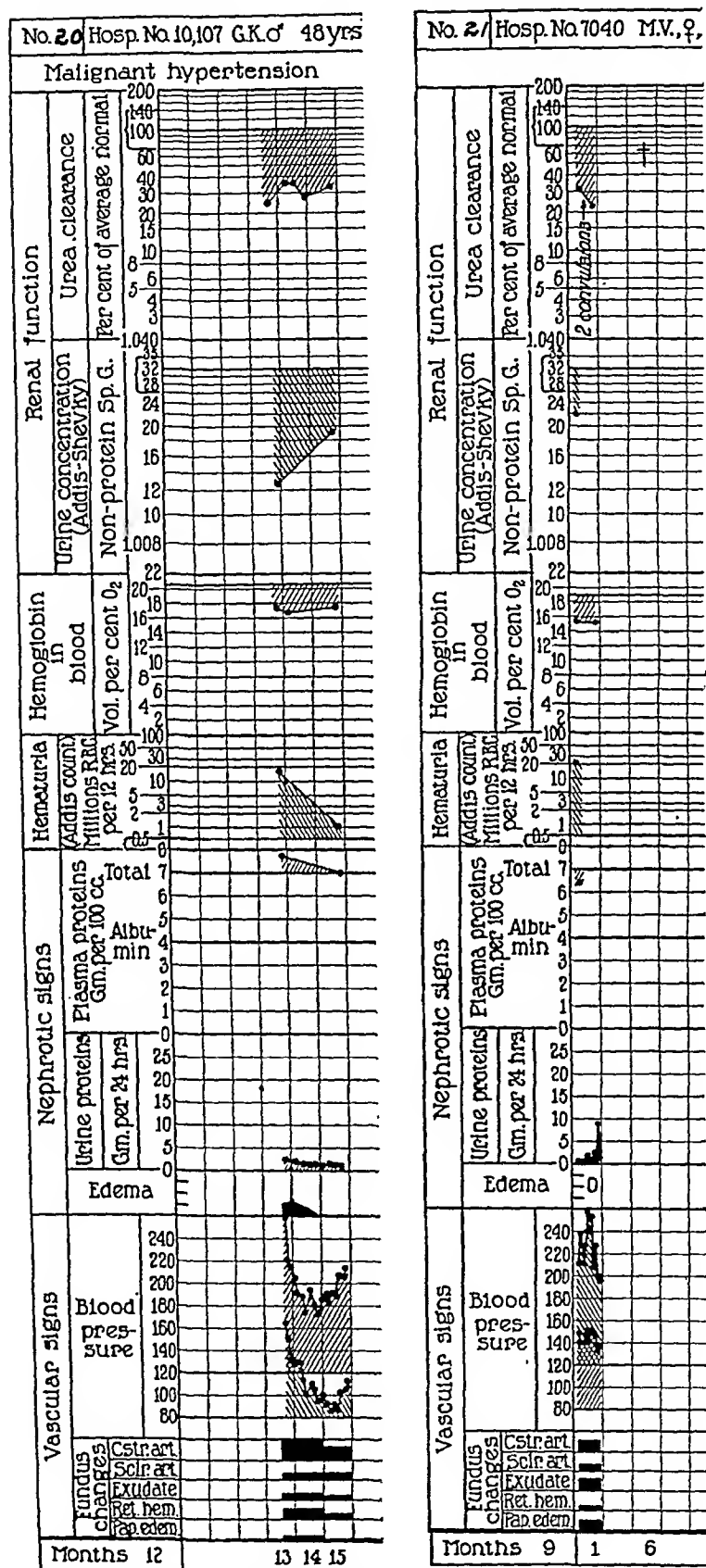


FIG. 10. Clinical and laboratory data depicting the course of malignant hypertension. Cases 20 and 21.



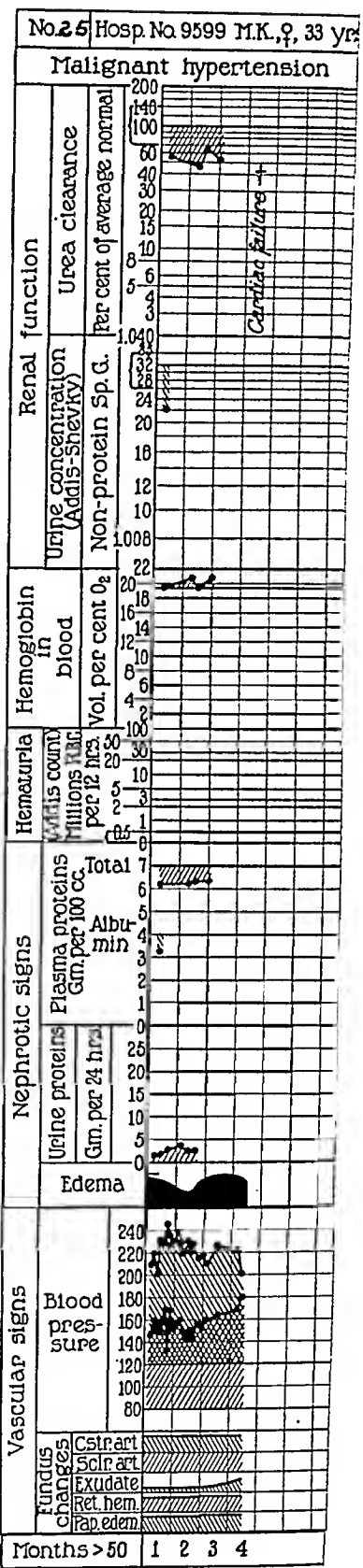
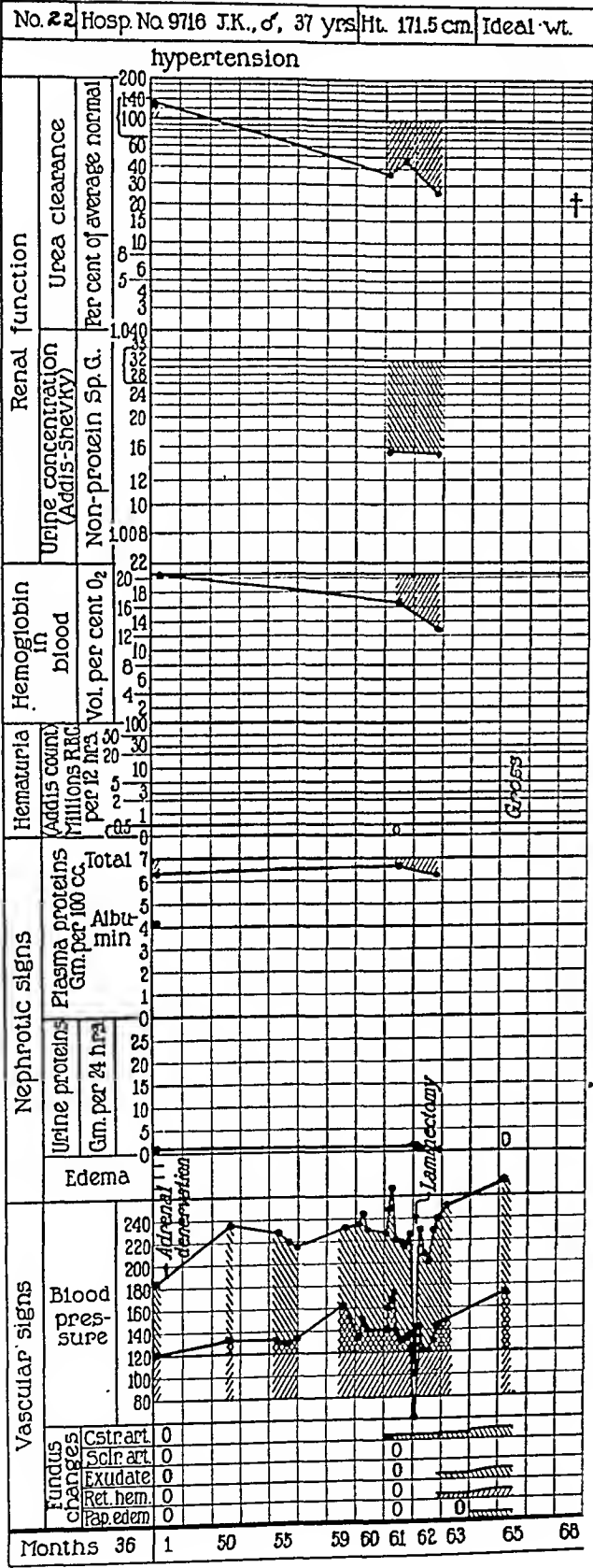


FIG. 11. Clinical and laboratory data depicting the course of malignant hypertension. Cases 22 and 25.

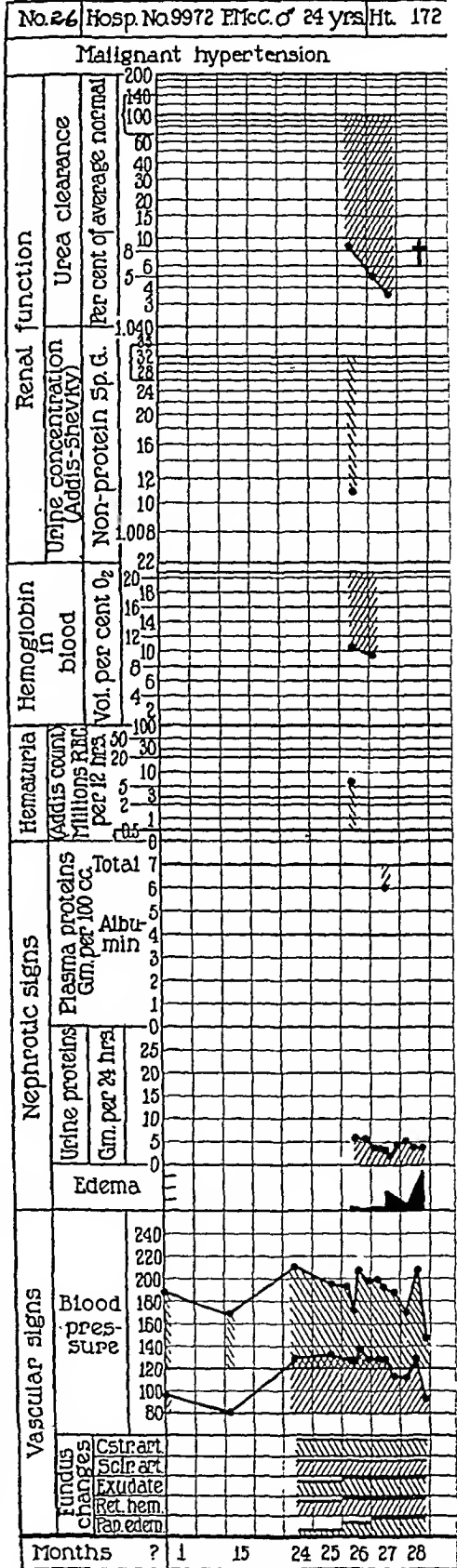
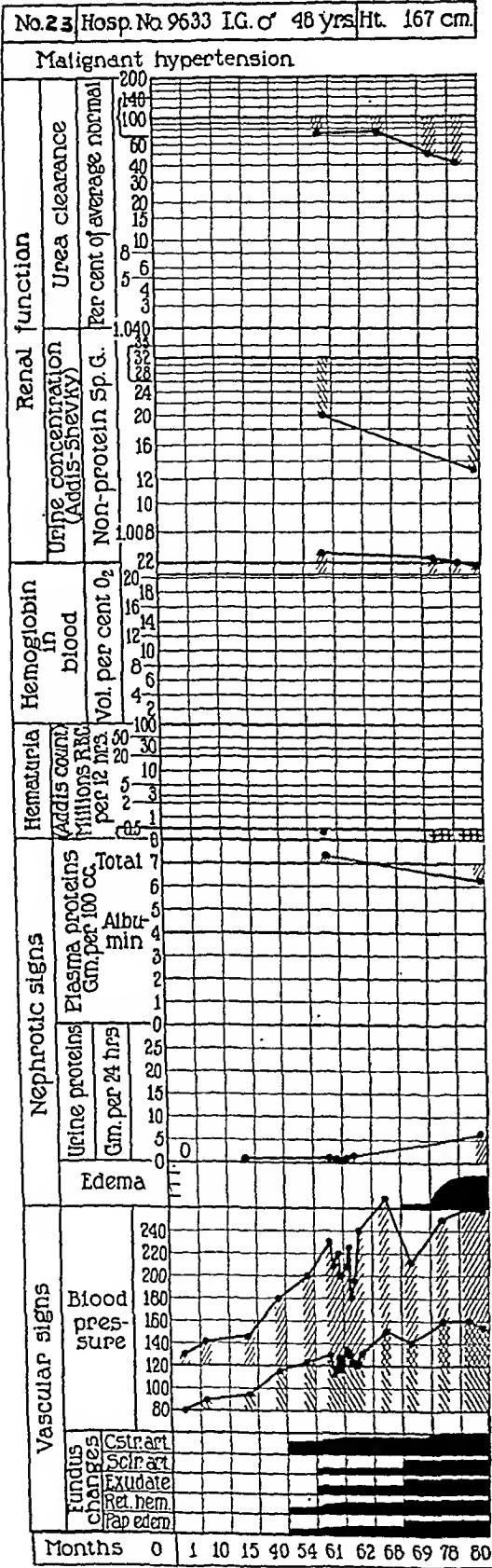


FIG. 12. Clinical and laboratory data depicting the course of malignant hypertension. Cases 23 and 26.

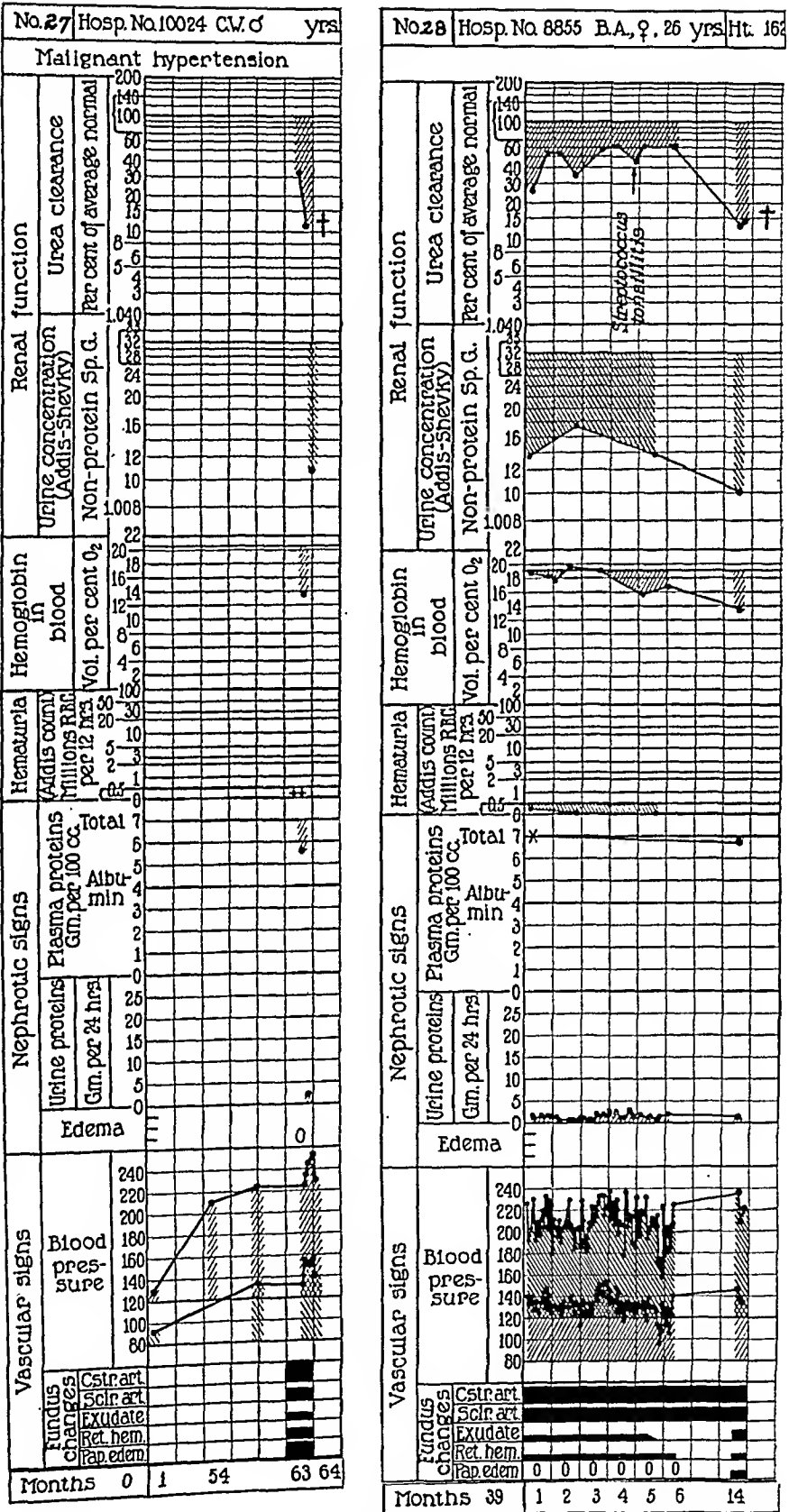


FIG. 13. Clinical and laboratory data depicting the course of malignant hypertension. Cases 27 and 28.

No. 29 Hosp. No. 10,144 M.W. ♀ 21 y												
Malignant hypertension												
Vascular signs		Nephrotic signs		Hematuria Addis count Millions RBC per 12 hrs	Hemoglobin in blood Vol. per cent O <sub>2</sub>		Renal function					
							Urine concentration (Addis-Shevsky)	Urea clearance	Per cent of average normal			
Fundus changes	Blood pres- sure	Urine proteins Gm. per 24 hrs	Plasma proteins Gm. per 100 cc. Total Albu- min	per 12 hrs	20 18 16 14 12 10 8 6 4 2	1.040 1.032 1.028 1.024 1.020 1.016 1.012 1.008 1.004 1.000 0.996 0.992 0.988 0.984 0.980 0.976 0.972 0.968 0.964 0.960 0.956 0.952 0.948 0.944 0.940 0.936 0.932 0.928 0.924 0.920 0.916 0.912 0.908 0.904 0.900 0.896 0.892 0.888 0.884 0.880 0.876 0.872 0.868 0.864 0.860 0.856 0.852 0.848 0.844 0.840 0.836 0.832 0.828 0.824 0.820 0.816 0.812 0.808 0.804 0.800 0.796 0.792 0.788 0.784 0.780 0.776 0.772 0.768 0.764 0.760 0.756 0.752 0.748 0.744 0.740 0.736 0.732 0.728 0.724 0.720 0.716 0.712 0.708 0.704 0.700 0.696 0.692 0.688 0.684 0.680 0.676 0.672 0.668 0.664 0.660 0.656 0.652 0.648 0.644 0.640 0.636 0.632 0.628 0.624 0.620 0.616 0.612 0.608 0.604 0.600 0.596 0.592 0.588 0.584 0.580 0.576 0.572 0.568 0.564 0.560 0.556 0.552 0.548 0.544 0.540 0.536 0.532 0.528 0.524 0.520 0.516 0.512 0.508 0.504 0.500 0.496 0.492 0.488 0.484 0.480 0.476 0.472 0.468 0.464 0.460 0.456 0.452 0.448 0.444 0.440 0.436 0.432 0.428 0.424 0.420 0.416 0.412 0.408 0.404 0.400 0.396 0.392 0.388 0.384 0.380 0.376 0.372 0.368 0.364 0.360 0.356 0.352 0.348 0.344 0.340 0.336 0.332 0.328 0.324 0.320 0.316 0.312 0.308 0.304 0.300 0.296 0.292 0.288 0.284 0.280 0.276 0.272 0.268 0.264 0.260 0.256 0.252 0.248 0.244 0.240 0.236 0.232 0.228 0.224 0.220 0.216 0.212 0.208 0.204 0.200 0.196 0.192 0.188 0.184 0.180 0.176 0.172 0.168 0.164 0.160 0.156 0.152 0.148 0.144 0.140 0.136 0.132 0.128 0.124 0.120 0.116 0.112 0.108 0.104 0.100 0.096 0.092 0.088 0.084 0.080 0.076 0.072 0.068 0.064 0.060 0.056 0.052 0.048 0.044 0.040 0.036 0.032 0.028 0.024 0.020 0.016 0.012 0.008 0.004 0.000	140 120 100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0	200 180 160 140 120 100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0				
									Edema	240 220 200 180 160 140 120 100 80	100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0	100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0
									Cstr. art.	100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0	100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0	100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0
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									Exudate	100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0	100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0	100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0
									Ret. hem.	100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0	100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0	100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0
Cap. edem.	100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0	100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0	100 80 60 40 30 20 15 10 8 6 5 4 3 2 1 0									
Months		>12	1	11	12	13						

[illegible]

FIG. 14. Clinical and laboratory data depicting the course of malignant hypertension. Cases 29 and 30.

## DISCUSSION

The diagnosis of malignant hypertension was made in these 30 patients when the following morbid changes were observed: (1) hemorrhage and papilledema in the eyegrounds, (2) normal or moderately reduced renal efficiency (unless the disease was of relatively long duration), (3) rapid advance of the morbid changes (table 3), (4) elevated arterial pressure often with immoderately high diastolic pressure, (5) normal or slightly reduced plasma proteins and hemoglobin.

From the results of this study an attempt will be made to describe the usual course of malignant hypertension. It appears to be a syndrome of varied origin. Both male and female human beings suffer from it, males more commonly. It is a disease of early middle age, but may occur in youth or late middle age, seldom in old age. As a rule, hypertensive-vascular disease in the family is not common. It is not unusual for these patients to have had scarlet fever.

The chief complaints are headaches, visual disturbances, fatigue. These may occur singly or together. Far less frequent are dyspnea, convulsions, fainting, weakness, precordial discomfort, and edema of the ankles.

Signs and symptoms referable to special organs of the body may or may not be present. As a rule striking contrast exists between the neurotic behavior of patients with essential hypertension and equable emotions of those with malignant hypertension. Those archaic emotional patterns which the physician has learned to associate with essential hypertension occur but are not usual.

The heart, in particular the left ventricle, is responsible for dyspnea, which is common especially when the patients exercise. Pains referred to the heart and palpitations are frequent.

The kidneys produce few symptoms. Nocturia is usual, but ordinarily not troublesome.

Nausea and vomiting occur often. Weight loss of severe grade is also usual. Simultaneous occurrences of these symptoms and signs bode ill for the patient's life.

Impressive both to patient and physician is the sudden occurrence of blindness in one eye due to hemorrhage. Events such as this commonly inaugurate the syndrome and point to the ubiquity of the vascular involvement. That hemorrhage may occur within weeks or months after beginning rise in arterial pressure there is no doubt.

The results of physical examination usually convince one that the syndrome is rapidly progressive and bears little resemblance to the chronicity of essential hypertension. Papilledema, hemorrhage, exudate, intense arteriolar constriction, edema, detachment of the retina, and secondary glaucoma all speak eloquently for the aggressive qualities of this morbid process. The heart may not have time to hypertrophy, but dilatation of marked degree is not unusual.

# THE PROBLEM OF RHEUMATISM AND ARTHRITIS

## REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1937

(Fifth Rheumatism Review) \*

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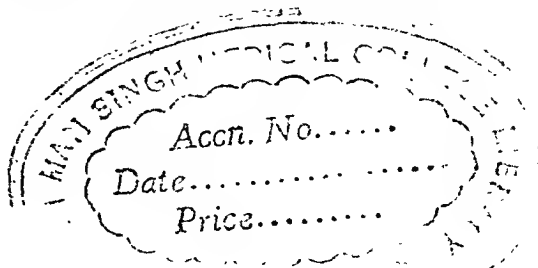
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##### Part I

*General Incidence of Rheumatic Disease; Social and Economic Importance.* The United States Public Health Service, accomplishing a National Health Survey in 1935-36, made a house-to-house canvass of some 800,000 families comprising 2,800,000 persons in 83 cities and 23 rural areas in 19 States. The results of this survey, just published,<sup>690</sup> indicate that among chronic diseases in the United States "*Rheumatism*" ranks first in

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*prevalence, second in producing disability, second in producing invalidity (permanent disability) and fourteenth in causing death.* Among the 127,000,000 persons in the United States there are 6,850,000 with "rheumatism": thus there are almost twice as many cases of rheumatism as of its nearest rival, heart disease (3,700,000 cases), more than 7 times as much rheumatism as "cancer and other tumors" (930,000 cases), 10 times as much rheumatism as tuberculosis in all its forms (680,000 cases), and more than 10 times as much rheumatism as diabetes (660,000 cases).

Rheumatism was responsible for more days lost from work (97,200,000 days) than any other chronic disability except "nervous and mental diseases" (which caused a loss of 132,500,000 days of work). More days of work were lost because of rheumatism than from heart disease (95,200,000 days). Rheumatism produced more than twice as much disability as tuberculosis (41,400,000 days) and made more invalids (147,600 persons permanently disabled) than any other chronic disease except mental and nervous diseases (which produced 269,300 invalids). Rheumatism produced more invalids than did heart disease (144,200 invalids) and twice as many as all types of tuberculosis (77,900 invalids). Compared to its morbidity, the mortality rate of rheumatism is low—even so it was fourteenth on the list of chronic diseases and annually it causes about as many deaths (4400) as do goiter and other thyroid diseases (4700 deaths annually).

In this national survey "rheumatism included arthritis, gout, neuralgia, neuritis, lumbago, etc." One can hardly minimize the significance of these figures by suggesting that perhaps most of the cases were of hypertrophic osteo-arthritis in the elderly, because 50 per cent of the surveyed group were under 45 years, and 70 per cent were under 55 years, of age. Half of those permanently disabled were under 55 years of age. Indeed the real menace of rheumatism is probably not less, but much greater, than these figures indicate for when one realizes that about 40 per cent of all cases of "heart disease" result from rheumatic fever (McLean, 1933), to the toll of "rheumatism" in its broadest sense should be accredited many more hundreds of thousands of victims of rheumatic carditis (840,000 patients, according to Paul, 1930) with their millions of days lost from work.

The chairman of the committee to propose a national health program to the President of the United States recently reported to him that annually about 1,500,000 persons in the United States are disabled by "arthritis" and an additional 1,750,000 persons are annually disabled by neuralgia, neuritis and lumbago (Roche). Thus, by all accounts rheumatism is still the chief contender for the title "King of Human Misery."

#### DEFINITION OF "RHEUMATISM"; CONTENT OF "THE RHEUMATIC DISEASES"

But just what is rheumatism and what are the rheumatic diseases? As Woods said, the layman is likely to apply the term "rheumatism" to "a

wide variety of painful conditions from carcinoma of the stomach, through renal calculus, pleurisy, chronic osteomyelitis and vascular degeneration to the lightning pains of tabes." Thus to the layman rheumatism is more or less any ache or pain not inside the head or abdomen. In general, however, he applies the term to painful affections of the locomotor apparatus; that is, diseases of the joints, muscles, ligaments and bones. Thus, the real basis for his designation is not etiologic or pathologic, but anatomic. Vague as this concept is, that of physicians is hardly more concise. In the national survey, "rheumatism included arthritis, gout, neuralgia, neuritis, lumbago, etc." Many will object to this grouping. Thus Crowe insists that gout and those forms of arthritis due to a specific microbe are not rheumatic. But although he tells us what rheumatism is not, he too must share the charge of ambiguity for he defines "chronic rheumatic arthritis" as "all the residue of joint disease which is left after the exclusion of an injured joint and a specific arthritis." To him, then, atrophic and hypertrophic arthritis and chronic periarticular fibrositis would apparently all be rheumatic. But asks Woods: "Except that both are arbitrarily called rheumatic what similarity does fibrositis with its protean manifestations and even more protean complications bear, for example, to morbus coxae senilis?"

The fundamental point to determine is this: Is there any well defined pathologic lesion, environmental or immunologic reaction, or physicochemical abnormality the presence of which stamps one disease as rheumatic and the absence of which indicates that another disease is not rheumatic? Although the editors have carefully read over 3000 papers in preparation for these five Rheumatism Reviews<sup>1-4</sup> we have found no satisfactory answer to that question.

The word "rheumatism," derived from the Greek word "rheum" or humor, was first used in early Latin and Greek writings in a rather nonspecific sense to indicate the flow of a noxious humor from one affected region to another, not necessarily to joints. Thus, in those days one could really speak of "rheumatism of the stomach." Later the term was used more specifically to designate disease due to flow of a rheum or humor to joints. In this special sense Ballonius (1643) first used the word "rheumatism" to describe rheumatic fever. Later the term was applied to other skeletal affections including painful conditions of muscles and fibrous tissues supposedly due to a discharge floating in the body. From time to time pathologists tried to describe some basic tissue lesion of rheumatism, a common denominator between the rheumatic diseases, which was supposedly a rather characteristic inflammatory reaction in fibrous tissue, especially in heart, skeletal muscles and joints, but this distinction has not been upheld by time. The nodular fibrous lesions in rheumatic fever, atrophic arthritis and fibrositis, although somewhat alike, are not indisputably identical; certainly they are absent in many conditions which physicians persist in calling rheumatic. Therefore Woods called the terms "rheumatism," "rheumatoid" and "rheumatic diseases" etymological nonsense.

If then there is as yet no accepted basic pathologic or physicochemical reaction pathognomonic of the rheumatic diseases, why do we persist in using such an unscientific term? Its continued use is not merely due to tradition;



it has survived because of its practicality. It is a handy label for a group of diseases which has acquired no better or shorter designation. By common understanding, the kernel of this disease-group consists of rheumatic fever, atrophic arthritis, myositis and fibrositis. But although this kernel can be fairly well defined, like an ameba with a shifting periphery, the term "rheumatism" has engulfed some foreign matter, diseases such as gout and "gonorrheal rheumatism," which have nothing in common with the kernel except that they involve the same structures, the locomotor apparatus, producing therein symptoms which at times may resemble those of "true rheumatism." In the last analysis, then, the concept of the physician largely resembles that of the layman. In reality physicians generally use the term "rheumatic diseases" in the same broad anatomic sense as do their patients.

The editors of these Reviews have always used the term "rheumatism" in a broad sense, preferring to foster a wide outlook on the problem. The "rheumatism service" of a hospital may be dedicated chiefly to the care of, let us say, patients with rheumatic fever, chronic arthritis and muscular rheumatism. But all too often the rheumatism service is the refuge for the patient whose skeletal aches and pains are really due to unsuspected hyperparathyroidism, or whose "sciatica" arises from a cord tumor, or ruptured intervertebral disk, or whose "rheumatic hip" represents a metastatic bone malignancy or multiple myeloma, or perhaps for the patient with the painful, stiff hands of scleroderma or with the sore muscles of dermatomyositis. Therefore it has seemed proper to discuss herein many conditions which admittedly have no remote etiologic connection with each other but are somewhat related in an anatomic sense. Hence, under the designation "diseases of joints and related structures," which for our purpose is more correct than the term "the rheumatic diseases," will again be included a review of whatever information would seem to be helpful to the physician whose patient is going to confront him, saying, "Doctor, I think I have rheumatism."

#### CLASSIFICATIONS OF DISEASES OF JOINTS AND RELATED STRUCTURES

The year 1937 was unique: practically no new classifications of rheumatic diseases were proposed! Aware of the difficulties involved, writers this year successfully repressed the almost irresistible urge to erect new classifications. A few writers offered sound criticism of existing classifications. The only real basis for an accurate classification and nomenclature is an etiologic one but so far this has been only partly possible. The next best classification would be one based on a study of morbid anatomy but even here knowledge is inadequate. Classification then must be largely clinical, supported by radiography. Fortunately such classifications are very useful but into them, whenever possible, should be introduced terminology based on such knowledge of etiology as we have (Woods). Warren, Hinton and Bauer have done this in their classification of joint diseases, as follows:

*A. Joint diseases of known etiology*

1. Traumatic; e.g., associated with internal derangement, fractures into joints, etc.
2. Infection; e.g., due to the gonococcus, tubercle bacillus, streptococcus and other organisms.
3. Neuropathic; e.g., associated with tabes, syringomyelia, leprosy.
4. Metabolic; e.g., associated with gout.
5. Constitutional; e.g., associated with hemophilia.
6. Anaphylactic; e.g., associated with serum sickness.

*B. Joint diseases of unknown etiology*

1. Degenerative joint disease (degenerative, hypertrophic or osteo-arthritis).
2. Rheumatoid arthritis (proliferative, atrophic or chronic infectious arthritis).
  - (a) Typical.
  - (b) Atypical (often called "nonspecific infectious arthritis" because the causative bacteriologic agent cannot be demonstrated).
  - (c) Spondylitis deformans, Strümpell-Marie or von Bechterew type, or rheumatoid arthritis of the spine.
3. Rheumatic fever.

[Since the causes of gout and hemophilia are unknown, some might object to the inclusion of gouty and hemophilic arthritis under the heading "joint diseases of known etiology." The distinction between typical and atypical rheumatoid arthritis will be discussed later under "atrophic arthritis."—Ed.]

According to Poynton, he who would separate the rheumatic diseases sharply is likely to be embarrassed by finding "border-line cases"; he who would link them all together, assuming a common diathesis, will be embarrassed to find that the classical examples of the various forms appear so different from one another that they must surely be entirely different in nature and causation.

## DISEASES OF JOINTS RELATED TO TRAUMA

In view of the frequency with which persons seek compensation for alleged traumatic arthritis, physicians should be familiar with accepted criteria for distinguishing true primary traumatic arthritis from non-traumatic arthritis affecting a joint subjected to subsequent trauma. In previous Reviews the criteria of others have been given. Those of Morrow are: (1) The trauma of a specific accident must be severe enough to produce acute inflammation (synovitis) of the affected joint—pain, swelling, effusion, dysfunction. (2) The traumatized joint must be the only one showing such inflammation. (3) It should be established that prior to the alleged injury articular function was normal, but the patient's statement to that effect does not constitute proof thereof. (4) Progressive articular changes may occur and in time be demonstrable clinically and roentgenographically; these changes should appear within a "reasonable limit of time," sometimes within six weeks, generally within three to six months. Any changes delayed 18 months or more after an accident can hardly be attributed to the accident. When posttraumatic intra-articular osseous changes do occur they are us-

ually hypertrophic in character, resembling those of ordinary senescent (degenerative, hypertrophic) osteo-arthritis.

Forms of chronic recreational, occupational or postural microtrauma which produce articular lesions were discussed by Bernstein and Fisher. To such trauma knees seem especially vulnerable. Although external, internal and crucial ligaments are powerful stabilizers of the knee joint they are inadequate to keep knees stable in every position; the support of surrounding muscles is even more important. Years after an acute articular injury the end results of old trauma may be hypertrophic villous synovitis and osteo-arthritis, with degeneration of cartilage and hypertrophy of marginal bone.

Athletic injuries most frequently affect knees; the common results therein were reviewed by Tucker. Direct violence to the knee may produce synovitis, contusion of the quadriceps muscles or their expansions with or without synovitis, prepatellar bursitis or bruising of the infrapatellar fat pad, or fracture of the patella or fibular head. Common results of indirect violence were synovitis from violent flexion or rotation of the knee, injury to lateral ligaments from lateral wrenches, and damage to the anterior cruciate ligament, infrapatellar fat and alar folds, posterior capsule or popliteus tendon after violent extension. The diagnosis of these different lesions was discussed.

Ochsner defined a simple, uncomplicated sprain as an injury to any or all of the articular components without fracture, rupture of a tendon, fragmentation of cartilage or persisting dislocation. The severity of pain, degree of discomfort and duration of incapacity from sprains vary greatly depending on such factors as the extent of the sprain, patient's age, obesity and muscle tone but especially on the treatment used. Unless treated promptly and efficiently an acute sprain may become chronic and persistently or intermittently painful for years. Permanent articular weakening with muscle atrophy may ensue, even limitation of motion or recurrent synovitis.<sup>21, 502</sup>

To study the pathologic histology of sprains, Miltner, Hu and Fang produced experimental sprain of varying severity in knee joints of rabbits. One week after mild sprains there developed articular swelling, synovitis (edematous membrane, focal hemorrhages, slight pannus, hydrops), edema, capillary congestion and cellular infiltration in subsynovial tissues, capsule and ligaments. Tissues were grossly normal in four weeks but microscopic evidence of inflammation persisted two weeks longer, ending in complete healing. [This suggests that sprained joints should be protected for at least two weeks after clinical signs have disappeared.—Ed.] A similar but more severe reaction was produced by more severe sprains. Injury to ligamentous insertions and fibrillar degeneration of surface layers of cartilage were seen. The inner, free portion of the semilunar cartilage on the traumatized side showed slight necrotic changes; after six weeks the distal free ends showed more advanced fibrillation with exfoliation of superficial cells and hyalinization of deeper cells. At the eighth and tenth weeks some specimens showed

complete degeneration of the free portion of semilunar cartilages. Cartilage heals slowly and incompletely; in certain cases the inflammation may become chronic and cartilage degeneration may predispose to changes in the more vascular articular structures with the full development of chronic traumatic arthritis.

*Laboratory Data.* Certain laboratory procedures help to confirm the diagnosis of acute traumatic arthritis. If anemia, leukocytosis, abnormal Arneth count and increased erythrocyte sedimentation rate are present, the condition is probably not traumatic arthritis. More valuable data can be obtained by analysis of synovial fluid. According to Collins the total polymorphonuclear leukocyte count of synovial fluid in acute traumatic arthritis is always less than 1000 cells, generally less than 500 cells, per cu. mm., whereas in atrophic arthritis it is always over 1000, generally over 5000 cells, per cu. mm. In acute traumatic arthritis the icteric index of synovial fluid is over 5 because of bilirubin from hemorrhage; in most inflammatory effusions it is below 5 (Kling). [Some cases of traumatic arthritis with hemorrhage into joints have an icterus index below 5.—Ed.]

The intra-articular injection of  $\text{CO}_2$ , air or other gas, or of some contrast medium such as abrodil, permits roentgenographic visualization of the soft parts within joints; this was considered valuable in the diagnosis of traumatic arthritis as it often promptly revealed lesions not otherwise visible, such as tears in the cartilage, hypertrophy of synovial membrane, narrowing or obliteration of the suprapatellar or infrapatellar spaces or posterior compartment of the knee due to adhesions or proliferation of tissue (Bernstein and Fisher; Kling).

*Treatment.* Much "chronic industrial rheumatism" is produced by delay in treatment or by inadequate treatment of traumatized joints in the earliest stages. It is most important to treat the earliest lesion by suitable rest, physical therapy, and the subsequent protection of the vulnerable joint from repeated injury (Collins). Significant effusions should be promptly removed by aspiration; this provides considerable relief and permits cytologic and chemical studies of the fluid so helpful in differential diagnosis. Kling and Sashin again recommended histamine ionization. Injured knees were treated by Tucker by variable amounts of rest, bandages and casts in the more severe cases, heat and massage, aspiration of effusions, faradic contractions, manipulative movements and above all special care to avoid undue wasting of the quadriceps muscle.

Tucker prescribes a schedule of graduated remedial exercises for affected knees. The first exercises avoid weight bearing: (1) twitching and contracting the quadriceps muscles for two minutes every hour while lying on a couch; (2) with knees bent and legs dangling over the edge of a couch, alternate extension and flexion of each knee, 20 such complete movements twice daily, increasing by 5 movements each time; (3) raising the extended leg by flexing the hip while lying flat; abducting the thigh at the hip, then adducting it; (4) bicycling as the patient improves; (5) as synovitis disappears weight-bearing exercises are prescribed: while holding the back of a chair, heel raising, knee bending and straightening; (6) skipping.

Bernstein and Fisher performed arthrotomy to remove hypertrophied synovial membranes, loose bodies and bony spurs.

The best treatment for simple sprains is proper strapping with adhesive; this provides adequate support and rest; Ochsner considered it "universally successful" but said, "few medical men seem to know how most effectively to apply the straps." Therefore Ochsner diagrammed the technic of applying straps to the commonly affected sites—ankle, wrist, knee, sacro-iliacs. He added a practical point regarding the removal of adhesive. Rather than using gasoline, kerosene, ether or other inflammable or explosive chemicals, the attendant should put about 1 teaspoonful of cold cream into the palm of one hand, rub the hands together for a moment and then rub the cold cream well into the adhesive plaster bandage which can then be removed with a minimum of discomfort.

The rôle of trauma in the pathogenesis of atrophic, hypertrophic and tuberculous arthritis, of diseases of the intervertebral disks, and of muscle affections will be discussed hereinafter in the sections devoted to these diseases.

#### GONORRHEAL ARTHRITIS AND GONORRHEAL "RHEUMATISM"

*Incidence.* Gonorrhea is much more prevalent than any other serious communicable disease. In the United States there are annually 1,037,000 cases of acute gonorrhea. In addition, similar number of patients seek treatment for chronic gonorrhea. There are constantly under observation and treatment 493,000 persons with gonorrhea in this country, and the disease is apparently not on the decline. A fourth of the patients are females; approximately 230,000 potential American mothers acquire the disease in each year. Such are the estimates of Vonderlehr and Usilton of the United States Public Health Service, based on its 1935 survey. Older statistics indicate that the joints of from 1 to 5 per cent of gonorrheal patients become infected. Thomas regards the lower figure as more accurate since gentler, less traumatizing treatment of urethritis became the vogue. Only one of Wishengrad's 251 male adults developed gonorrheal arthritis. Only three of Wilson's 76 adult female patients developed joint pains; none had true arthritis. However, two (7 per cent) of Drummond's 28 adults had "joint involvement." According to Benson and Steer who summarized the combined statistics of others, arthritis occurred in 15 (2.6 per cent) of 565 cases of gonorrheal vaginitis in children. But no arthritis developed among 68 girls with lower genital tract infection treated by Reichert, Epstein, Jung and Colwell.

Why do some patients develop, others escape, articular complications? According to Pelouze, metastatic complications such as arthritis are preponderantly the result of trauma to the urogenital focus: "One has but to survey the treatment accorded patients or to study the patient's doings prior to the onset of arthritis to demonstrate the truth of this statement." Thus Keefer and Spink<sup>365</sup> noted articular exacerbations after vigorous prostatic

massage. Another writer<sup>660</sup> suggested a different hypothesis: In persons of the "acid type" (who eat too little calcium-containing food and prefer acid condiments and those foods which yield an acid residue) gonorrheal urethritis "is associated with further toxic effects which cause a constitutional disturbance such as allows of the development of a coincident protozoon and it is this which is responsible for the gonorrheal arthritis."

[This statement is given without proof of any sort.—Ed.]

*Clinical Data: Criteria of Diagnosis.* Criteria for a diagnosis of proved gonorrheal arthritis, as used by Keefer and Spink,<sup>365</sup> were: (1) a history of recent gonorrhea; (2) evidence of genital gonorrhea; (3) a positive gonococcus complement fixation test on blood or on synovial fluid or both; (4) a demonstration of gonococci in synovial fluid. The criteria of Warren, Hinton and Bauer for "proved gonorrheal arthritis" were: (1) a history or physical evidence of previous or existing gonorrhea, (2) a history of joint disease consistent with recognized characteristics of gonorrheal arthritis, (3) the isolation on smear or culture of gonococci from the primary focus or synovial fluid. "Probable gonorrheal arthritis" can be diagnosed when the first two criteria are present but the third absent.

[These criteria are exact as research demands, but these authors noted cases in which, because of the absence of some of the usual clinical features, diagnosis was particularly difficult until the eventual discovery of gonococci in joints, blood stream or both. Whenever possible these criteria should be used in general practice but when bacteriologic or serologic tests are negative or unavailable, yet the patient presents a genital infection, or recent history thereof, and acute arthritis of the type hereinafter described, a presumptive diagnosis is justified, certainly to the extent that a therapeutic test should be instituted at once; a prompt response greatly strengthens the presumption.—Ed.]

*Symptoms and Course.* In an excellent survey of 140 proved cases of gonorrheal arthritis Keefer and Spink described its features. Although described in previous Reviews we shall summarize them briefly because, with the advent of the new highly successful methods of treatment, early recognition of gonorrheal arthritis is especially important.

Generally within 10 to 20 days (but occasionally much later<sup>645</sup>) after the onset of genital (less frequently conjunctival or rectal) gonorrhea, acute arthritis appears, often abruptly, and more often polyarticular than monarticular. Fever and leukocytosis (generally moderate) and an elevated erythrocyte sedimentation rate are usually present. Curiously a respiratory infection often precedes the arthritis; in connection with febrile polyarthritis this often leads to an erroneous diagnosis of rheumatic fever. Articular and periarticular inflammation are generally intense. Any joints may be affected, most often knees, ankles and wrists. These joints are often involved in an intense tenosynovitis without definite arthritis. Juxta-articular muscles may waste rapidly without histologic evidence of acute inflammation therein. Since acute tenosynovitis occurs more often with gonorrheal than with any other type of arthritis, its presence should arouse suspicions of gonorrhea. First polyarticular and often migratory, the arthritis may soon become stubbornly monarticular. The acute process lasts from a short time to several weeks or longer. The commonest "complication" (which occurred in 15 per cent of the 140 cases) is conjunc-

tivitis which may appear with the arthritis or appear and disappear before the arthritis; the conjunctival exudate reveals no gonococci.

Of the 140 patients of Keefer and Spink, 104 were in males, 36 females; 107 of the cases were polyarticular, 33 monarticular. The following joints were affected (numbers refer to cases): knees 127, ankles 56, wrists 44, fingers 31, metacarpophalangeal 27, metatarsophalangeal 27, shoulders 25, hips 23, elbows 20, toes 19, lumbar spine 14, sacro-iliacs 8, heels 7, cervical spine 6, dorsal spine 4, sternoclavicular 3, temporomandibular 3, costosternal 2, acromioclavicular 1, olecranon bursa 1. Teno-synovitis affected ankles in 32 cases, wrists in 19, metacarpophalangeal in 6, metatarsophalangeal in 6, knees in 4 and fingers in 4 cases. Abscess of a tendon sheath occurred twice. Iridocyclitis, a serious complication which may impair vision, occurred in 4 cases. Death occurred in 7 of the 140 cases, three times from inter-current pneumonia, twice from endocarditis, once from glomerulonephritis and once from "progressive gonococcic infection."

*Unusual Features and Complications.* Several reports described unusual complications of gonorrheal arthritis. A young female patient of Sloane and Sloane developed gonorrheal arthritis of a knee and hip. Acute intrapelvic protrusion of the femoral head into the acetabulum (Otto pelvis) developed and progressed in spite of treatment by traction and splints. Bacteremia *without* endocarditis was present in three cases of Keefer and Spink. It was associated with a striking cutaneous eruption, maculopapular, in some areas hemorrhagic, rapidly becoming vesicular, then pustular. It was most intense over extremities and was never seen without bacteremia. Hazel and Snow noted a case of gonococcic septicemia without endocarditis but with arthritis and a generalized purpura with the petechiae more marked on palms and soles. Reviewing the literature Gillespie and Thompson concluded that culturally proved cases of gonorrheal endocarditis are rare; they reported three such cases (two with arthritis) with cultural and necropsy data, an incidence of 0.15 per cent of 1947 cases of gonorrhea. Petechiae were present in skin, pericardium and pleura. A patient of Cromer with gonococcal endocarditis (clinical diagnosis) slowly recovered after several transfusions. Williams noted two such patients; one died, the other rapidly recovered after two sessions of fever therapy. The patients of Cromer and of Williams exhibited petechiae described as "small red sore spots" or slightly tender, circumscribed, purplish red areas, 2 mm. to 1 cm. in diameter, chiefly on extremities; many showed a central white area of necrosis; a few showed vesiculation with seropurulent fluid. Two of Keefer and Spink's <sup>365</sup> patients developed gonococcic endocarditis and died. Only nine cases of gonococcal aortitis have been reported; Nichol and Dobrin described a case of gonorrheal arthritis with acute gonococcal aortitis and aortic endocarditis, multilocular aortic aneurysm and a congenitally bicuspid aortic valve.

Keratoderma blennorrhagicum affected four of Keefer and Spink's cases of gonorrheal arthritis. Acute hemorrhagic glomerulonephritis may accompany gonorrheal endocarditis. It is rarely seen without endocarditis but Keefer and Spink noted it in two cases of gonorrheal arthritis without endocarditis; one patient died, cultures of the kidney were sterile.

The diagnostic significance of the more common "complications" was emphasized by Keefer and Spink. Conjunctivitis may accompany post-dysenteric arthritis, rarely rheumatic fever, but most commonly gonorrheal arthritis. Hence, acute arthritis with conjunctivitis or with keratoderma suggests gonorrhea. Acute polyarthritis with tenosynovitis, a history of gonorrhea, conjunctivitis or iridocyclitis and a cutaneous eruption should always suggest that the arthritis is gonococcal.

*Pathology.* No new data on articular pathology were presented. Keefer and Spink summarized the studies of Keefer, Parker and Myers<sup>2</sup> (1934).

*Roentgenograms.* No new studies were reported.

*Laboratory Data.* "Smear-method." The inspection of smears of genital or other exudates properly stained by Gram's method has many merits; it is simple and inexpensive; the report can be obtained in a few minutes; smears on glass slides are easily transportable. They are unreliable when stained with methylene blue. The smear method is much less dependable in chronic cases, when few gonococci and many secondary invaders are present. Unfortunately there is no uniformity in making or staining smears in our public health laboratories. Such were the conclusions of Carpenter who, as a Committee Referee, reported to the American Public Health Association the Committee's approved methods of obtaining, examining and interpreting smears and cultures.

2. Cultures. The cultural method of McLeod and his associates (1934) is "the most reliable available procedure for diagnosing gonococcic infection." The technic was redescribed.<sup>100, 101</sup>

3. Gonococcal complement fixation test. Some regard this test as unreliable; others consider it sufficiently reliable for routine use. Warren, Hinton and Bauer performed 614 tests on serums from 316 patients with various types of arthritis and concluded that it was an important diagnostic aid. Of 125 tests in 74 cases of proved or probable gonorrheal arthritis 82 per cent gave positive reactions at some time during the arthritis; only 18 per cent were negative. Consistently positive reactions on every test were found in 81 per cent of 52 "proved cases" and in 64 per cent of the probable cases of gonorrheal arthritis. Of 239 cases of nongonorrheal arthritis, 92 per cent gave consistently negative reactions. The test was also approved by Cohn, who made 1153 tests on 495 patients with proved or suspected gonorrhea (only seven with arthritis). Keefer and Spink found positive reactions in blood in 85 per cent of 83 cases of gonorrheal arthritis, and in synovial fluid in 66 per cent of cases. Tests on synovial fluid were never positive unless those on blood were positive; the latter were more reliable and more frequently positive.

In interpreting the test the following must be remembered.<sup>127, 701</sup> The production of complement fixing antibodies is dependent on the duration and spread of the infection. In acute, uncomplicated cases of gonorrhea localized to the superficial urethral or cervical mucosa, the test may be negative as insufficient antibodies are



absorbed. In acute complicated cases, such as cases of arthritis, the test is generally strongly positive. The test is not as specific as the Wassermann reaction and is far more delicate. The present technic is not sufficiently accurate for one to rely on any one test or even on repeated tests in a given case; tests should be interpreted only in association with clinical and bacteriologic features. Some cases of proved or probable gonorrheal arthritis and some of nongonorrheal arthritis give intermittently positive and negative tests. There is a 10 per cent chance that any positive test is falsely positive. Since a negative test occurs in about 20 per cent of gonorrheal cases, a negative reaction does not entirely rule out gonorrhea. The test may be negative even in proved cases of gonorrhea because it may have been done prior to the appearance of antibodies (it generally takes 10 days to 4 weeks, occasionally 5 to 24 weeks, after the initial infection for enough antibodies to accumulate in the blood to give a positive test) or because it may have been done after the disappearance of antibodies. Some patients in the last stages of infection lose the power of producing them. A test may be negative because of imperfections in the method or because the antigen employed may not have been prepared from enough different strains and may not contain the strain infecting a particular patient. According to Tulloch (1922) there are five chief antigenic strains of gonococci; 72 per cent of all cases are produced by one main strain. In the past the antigens used have not had a sufficiently wide range of activity. Warren, Hinton and Bauer used 4 strains; Cohn used 12 strains.

Comparative value of smears, cultures and complement fixation tests. Of 92 patients with a history and symptoms of gonorrhea Carpenter obtained positive smears in 38 per cent, positive cultures in 50 per cent, and positive complement fixation tests in 87 per cent. Nevertheless he considered complement fixation tests unreliable because false positive reactions were obtained in 71 per cent of 28 patients without evidence of gonorrhea by history, symptoms, examination, cultures and smears. [This percentage of false positives is much higher than that obtained by others.—Ed.] Furthermore, extremely variable results were obtained on sera of the same four patients when sent to eight different laboratories. Carpenter admitted, however, the test was likely to be much more reliable and valuable in cases of metastatic infection, such as arthritis.

4. Synovial cytology, chemistry. One hundred fourteen samples of synovial fluid from 83 patients with gonorrheal arthritis were examined (Keefer and Spink<sup>365</sup>). In 26 per cent of 78 cases the fluid was culturally positive; in 74 per cent the fluid was sterile. The total cell count per cu. mm. was 7000 to 236,000 in the former; 1600 to 120,000 in the latter. The total protein content was that of an exudate in both types (3.5 to 6.0 gm. per 100 c.c.). The nonprotein nitrogen was the same as in blood. Infected synovial fluid contained less sugar, sterile fluids contained the same amount of sugar as blood.

5. Bactericidal tests of blood and synovial fluid. Spink and Keefer<sup>363, 643, 644</sup> noted that during a gonococcic infection bactericidal antibodies against the homologous infecting strain appear in the circulating blood. Their interpretation follows. They probably represent the patient's defensive response to his infection and are largely responsible for localizing and killing the infection. They increase during the course of gonorrhea or gonorrheal arthritis. When enough specific antibodies have developed to kill the infecting organisms, articular repair proceeds. Gonococci are killed in vitro by lysis produced by sensitization of bacteria by antibody. Then destruction is completed by complement. Phagocytosis of bacteria is not an important feature. Serum agglutinins do not develop and agglutination tests are of no value in diagnosis or in studying the immunity mechanism in gonorrhea. The bacteriolytic antibodies diffuse from blood into synovial fluid. In sterile joint fluids the antibacterial antibodies are present in amounts equal to or slightly less than in blood; but in patients with infected joint fluid the fluid contains no bactericidal anti-

bodies and that of whole blood is low or only moderately elevated. When gonococcemia is present no bactericidal antibodies are found but when the bacteremia ceases antibodies appear in blood. Thus the prevention of bacteremia seems to depend on the antibody content of blood or on an efficient local defense reaction in the primary focus of infection.

Keefer and Spink noted that gonococci localize and survive in areas amply supplied with mucin; e.g., in urethra, cervix, conjunctiva and joints. Perhaps mucin is a favorable medium for gonococci or somehow helps them survive. It was found that synovial mucin assists some strains of gonococci to survive, especially when synovial fluid antibodies are low. But when the antibody content of synovial fluid is high, synovial mucin does not prevent the bactericidal action of the fluid. Synovial fluid also contains antitryptic substances which probably protect cartilage from destruction by the tryptic-like ferments of leukocytes.

*Diagnostic Value of Laboratory Tests.* In cases of typical gonorrheal arthritis diagnosis is relatively easy. In other cases diagnosis may be difficult because the arthritis may appear long after an initial genital infection or because the disease may mimic other arthritides.

Case reports were given illustrating these difficulties and the usefulness of laboratory tests therein (Warren, Hinton and Bauer; Spink and Keefer<sup>645</sup>): cases of acute polyarthritis, later proved to be gonorrheal, in women unaware of latent, persistently asymptomatic genital infection; cases of proved gonorrheal arthritis in men who had not had acute genital gonorrhea within 18 months to 5 years and in whom during arthritis no genital gonorrhea could be found; cases of gonorrheal arthritis preceded by respiratory infection in patients, unaware of genital infection—hence simulating rheumatic fever; cases in which proved acute gonorrheal arthritis developed during pregnancy in women with or without discoverable genital gonorrhea.

In such cases the combination of close clinical observation and laboratory aids is necessary. Sometimes preliminary laboratory tests may be misleading but a suspicious clinical picture will force one to continue the eventually successful search for positive laboratory data. In other cases the clinical picture may be misunderstood and a complement fixation test, done routinely in difficult cases, may provide the first clue to the true nature of the disease. In other words the starting point for an accurate diagnosis must be a healthy suspicion of the presence of gonorrhea, which initiates the proper correlation of clinical and laboratory observations. An aid to the development of the proper suspicion is the realization that "the gonorrhea patient is perhaps the most inveterate liar in the realm of medicine."<sup>733</sup>

It would appear, however, that the matter of suspicion can be considerably overdone, for one physician<sup>108</sup> wrote: "It is my belief that gonococci are responsible for considerable of the muscle and joint pains in patients over forty. For the past ten years patients over 40 complaining of vague aches and pains of muscles or joints have been routinely given mixed gonorrheal vaccine. The results have been just about 99 per cent perfect—with either complete cessation of symptoms or marked improvement. . . . Cases of osteo-arthritis, myalgia, tenosynovitis report an increase of symptoms the day following injection and then steady improvement. I give this treatment regardless of venereal history."

[This is carrying suspicion to the nth degree!—Ed.]

## TREATMENT OF GONORRHEAL ARTHRITIS

The past six years have seen the development of the two greatest advances ever made in the treatment of gonorrhea and gonorrheal arthritis: the use of fever therapy (1932 et seq.) and more recently the use of sulfanilamide.

*Fever Therapy for Gonorrheal Arthritis.* During 1937 about 15 reports presented the results of fever therapy in about 380 cases of gonorrheal arthritis. Bierman, Horowitz and Levenson reported further experiences with their "combined heating technic." Systemic fever ( $106.5^{\circ}$  F. for 12 to 14 hours) was accomplished by short wave diathermy; during six to eight hours of this fever the pelvic temperature was increased to  $108$  to  $110^{\circ}$  F. by the use of pelvic diathermy electrodes. Especially for women does this technic provide a superior method of curing genital as well as articular infections.<sup>53</sup> One report<sup>51</sup> noted results in 31 cases of gonorrheal arthritis: there was "complete restoration of joint function" in 26 cases (84 per cent); no improvement in 3 cases in 2 of which bony ankylosis required arthroplasty; 2 patients were lost sight of. A later report<sup>54</sup> summarized their total results (overlapping series 1935-1937): In 80 per cent of 40 cases of acute or chronic gonorrheal arthritis, previously treated unsuccessfully by other methods, "joint symptoms subsided with remarkable uniformity immediately after the termination of (an average of three) treatments."

Seventeen patients with gonorrheal arthritis (duration unstated) were treated by Potter, Redewill and Longley. From 5 to 10 weekly sessions of fever (8 hours at  $103$  to  $105^{\circ}$  F.) were given: "all cases showed rapid improvement and remarkable cures" even those in which the disease had lasted a year or more. [In our experience gonorrheal arthritis rarely remains active this long; in such cases the diagnosis should be reconsidered.—Ed.] It was believed that the intravenous injection of "mercurochrome 1 per cent in glucose 50 per cent" aided patients to respond to hyperpyrexia. Doses were given on three alternate days during six days prior to the sessions of fever. [No control studies were reported and no evidence was given to substantiate this opinion.—Ed.]

Forty patients with gonorrheal arthritis (duration unstated) were given two to four sessions of fever, each of six hours at  $106$  to  $107^{\circ}$  F., by Newman and Berris: 30 (75 per cent) of these patients were "completely cured"; marked improvement was noted in 4 cases with bone destruction but short wave diathermy and massage for two months were required to restore good function. Thomas treated 53 patients: of 48 who had acute conditions, 46 (95 per cent) were promptly "symptomatically cured"; 5 patients with "chronic gonorrheal arthritis" were "markedly relieved." Purcell's two patients with acute gonorrheal arthritis were also "completely relieved."

Of 23 patients with gonorrheal arthritis (duration unstated) treated by Simmons with fever therapy 15 (66 per cent) were promptly "cured" (complete cessation of pain and inflammation but not necessarily complete return

of normal function). After fever gonococci were found in urethral smears in only 2 of these 15 cases. There was "marked relief" in 4 cases (17 per cent), little or no relief in the remaining 4 cases (17 per cent), probably because of inadequate fever. It was concluded that a minimum of 25 hours of fever (106 to 107° F.) is necessary to cure most cases.

[Some believe that this amount of heat is often not required.—Ed.]

Two girls, aged 13 and 3 years, with acute gonorrheal vaginitis and arthritis were markedly improved by 1 and 2 sessions of fever respectively, given by Spekter and McBryde. Forty-three patients were treated by Gwynn: arthritis had been present for 1 week to 5 years; in 24 cases it was acute (8 weeks or less). Results were not summarized in the usual manner but "the average improvement of the entire group was 90.2 per cent." Most of them had been unrelieved by other treatments prior to fever therapy; all but one had "negative" urethral smears after fever therapy. Simpson and Kendall have now treated 47 patients with acute and 28 patients with chronic (8 + weeks) gonorrheal arthritis: "All evidence of active arthritis was abolished in all cases." In 67 cases (89 per cent) all evidence of genito-urinary infection disappeared during treatments (three to five sessions of fever, each five to seven hours at 106 to 107° F.). All of four patients treated by Cheetham and Roemer were cured after one to six sessions of fever.

[To obtain a normally functioning joint the disease must be cured before permanent damage takes place; unfortunately the latter may occur within two to three weeks.—Ed.]

Pettit favored the use of short (three to four hours) sessions of fever (105 to 107° F.) induced by hot water baths for the treatment of genital gonorrhea, especially of pregnant women, but his results in gonorrheal arthritis were not good: of four patients treated one was cured, one markedly improved; two (50 per cent) were not improved.

[Apparently amounts of fever were inadequate.—Ed.]

Schnabel and Fetter reported their further experiences: of 49 patients with acute gonorrheal arthritis (less than six weeks' duration) 37 (76 per cent) were "cured," 7 (14 per cent) were markedly improved, 5 (10 per cent) moderately improved. The average period of hospitalization for the 49 patients was 22 days after fever therapy was begun. Of 21 chronic cases, in which the average duration of symptoms was 6.3 months, in 5 cases (24 per cent) the patients were cured, in 8 (38 per cent) markedly, and in 8 (38 per cent) moderately, improved. The average period of hospitalization in these 21 chronic cases was 35 days after fever therapy was begun. To prove that fever therapy was a superior method, an equal number of patients treated by other means than fever was studied. Of 49 patients with acute conditions treated *not by fever* but by physiotherapy to joints and local chemotherapy to genital lesions, only 4 (8 per cent) were cured

(compared to 37 cases or 76 per cent of the fever-treated group) and 45 improved. Of 21 patients with chronic conditions *not* treated by fever therapy, only 1 (5 per cent) was cured (compared to 5 cases or 24 per cent of the fever-treated group); 19 were improved and one died. The average period of hospitalization in cases in which fever was not used was just twice as long in the acute cases (45 days) and  $3\frac{1}{2}$  times as long in the chronic cases (156 days) as it was in those in which fever was used.

[This report deserves special commendation as it is the first one in which such a comparison has been made.—Ed.]

In five cases acute gonorrheal arthritis was promptly cured by Solomon and Kopp. Brodribb treated four patients with acute gonorrheal arthritis or fibrositis "with great success"; all obtained immediate relief from pain.

[The latter report includes a comprehensive review of fever therapy, its methods, indications and results, and is notable because it apparently represents the first British report on results in gonorrheal and nongonorrheal arthritis.—Ed.]

A patient with acute gonorrheal tenosynovitis of a foot was successfully treated by incision and drainage of pus and by two applications of radiotherapy (Reeves).

*Summary.* The results given in these 15 reports agree with those noted in previous Reviews<sup>3, 4</sup>; indeed they are somewhat better, as might be expected with further experience and the use of higher temperatures for longer periods. Thus, about 90 per cent of these 380 (circa) patients with acute or chronic gonorrheal arthritis were "cured," made symptom-free. Fever therapy was regarded as a "specific,"<sup>561</sup> "the procedure of choice,"<sup>270</sup> "the best treatment now available,"<sup>619</sup> "the treatment of choice to be used at the earliest available opportunity"<sup>54</sup> in gonorrheal arthritis. In such cases "the proper application of fever therapy should be the first thought."<sup>673</sup> Results were of course better in acute than in chronic cases where irreparable articular damage had often already occurred. In some cases poor results were obviously due to inadequate amounts of fever. In general, sessions of fever consisted of five to six hours at 106 to 107° F. (rectal). Usually three or four, occasionally only one or two, sessions of fever were required, given at intervals of three to five days. Since a certain percentage of patients continue to give "positive urethral smears," even after joints have been cured by fever, the "combined method" of general and local heating described by Bierman and his colleagues, seemed especially indicated in cases of resistant local infection.

#### FEVER THERAPY FOR NONARTICULAR GONORRHEA

The beneficial effects of fever therapy on gonorrhea without arthritis were given in a number of reports. Most patients were promptly cured.<sup>20, 497, 543, 555, 641, 723</sup>

Thus, 93 per cent of 121 women with gonorrhea treated by Bierman and Horwitz became "gonococcus-free" after an average of two treatments. Results in

172 cases of Potter, Redewill and Longley were generally excellent except in cases of chronic posterior urethritis. Of 189 patients of Desjardins, Popp and Stuhler, 90 per cent were "cured"; 10 per cent were improved in varying degrees. Results were better when sessions of fever were given closer together, every third day, and were longer, at first five or six hours, later eight, ten or twelve hours. In 90 per cent of the cases, from one to five treatments were needed, in 10 per cent from five to ten sessions were required to eradicate gonococci. All evidences of gonorrhea were abolished by fever therapy alone in 92 per cent of Simpson and Kendall's 38 cases, given an average of four sessions of fever, five to seven hours each.

Of particular interest was the report of Parsons, Bowman and Plummer: 43 patients were given fever therapy; 44 others were treated by older methods. Eleven in each group had "acute gonorrhea": 73 per cent of each group were cured but it took only 27 days (av.) in the first group, 81 days (av.) in the others. Fourteen in each group had acute prostatitis with complications: 86 per cent of those given fever were cured in an average of 22 days; 71 per cent of those treated otherwise were cured in an average of 84 days. The remaining 37 patients had chronic prostatitis with complications: 89 per cent of 18 given fever were cured in an average of 28 days; only 32 per cent of the 19 treated otherwise were cured and it took an average of 105 days.

However, only 6 of the 10 patients of Cheetham and Roemer were cured of urethritis after an average of 4 sessions of fever, 5 to 6 hours at 105.5 to 106° F. Because of similar failures to cure gonococcic infections by a single or by repeated short sessions of fever, Warren, Scott and Carpenter used one session of fever at 106.7° F. (41.5° C.), long enough to kill each patient's particular strain of gonococcus (av. 14.8 hours); of 31 patients so treated, 81 per cent were cured. The procedure was not devoid of risk; one patient died. Because estimations of the thermal death time of each patient's gonococcus are difficult and generally impracticable, Simpson and Kendall advocated one 10 hour session of fever; preliminary results indicated that most patients will respond favorably to such single sessions. "One-treatment cures" were also obtained by Bierman and Levenson who applied "combined heating" for 12 to 14 hours.

[Although single sessions of fever of more than 10 hours' duration may be successful they increase materially the responsibilities of the physician and the risk to the patient. It now seems likely that the use of sulfanilamide, alone or combined with short sessions of fever, may obviate the necessity of long sessions.—Ed.]

#### FEVER THERAPY FOR GONOCOCEMIA AND GONORRHEAL ENDOCARDITIS

Warren<sup>702</sup> reported one case in which gonorrheal septicemia was cured by prolonged fever therapy. Hazel and Snow also cured a patient with gonococcic septicemia, purpura and arthritis by two sessions of fever, each of 5 hours, at 105.6 to 107.8° F. A patient with gonococcal arthritis, severe sepsis and probable gonococcal endocarditis (but with negative blood cultures) recovered promptly after three sessions of fever given by Williams. In another case of Williams, results were unsuccessful: a patient with proved gonococcal endocarditis and arthritis died of syphilitic cirrhosis of the liver and uremia although the blood was sterilized from the fever. Repeated sessions of fever, given to a patient with gonococemia, seen by Krusen and Elkins, temporarily sterilized the blood but the patient died of endocarditis and nephritis.

## GENERAL REMARKS ON FEVER THERAPY

*Historical aspects* of the development of fever therapy and notes on the various means of producing artificial fever were reviewed by several.<sup>51, 75, 334, 525, 544, 564, 586, 614, 622, 638, 941</sup>

Physicians indicated their *preferences for different methods* of producing fever: by the Kettering hypertherm,<sup>279, 699, 619, 922, 673</sup> General Electric Fever Cabinet,<sup>111</sup> Kimble Cabinet,<sup>551, 594</sup> diathermy,<sup>613</sup> electromagnetic induction,<sup>25, 597</sup> air-conditioned cabinets with electromagnetic induction,<sup>498</sup> preheated cabinets,<sup>497</sup> radiant energy cabinets,<sup>941</sup> humidified heated cabinets,<sup>555</sup> inductothermy,<sup>25, 614</sup> hot water bath,<sup>543, 578</sup> short wave therapy,<sup>288, 339, 384, 737</sup> vapothermy,<sup>506</sup> "blanket-method."<sup>217</sup> Evidence required by the Council on Physical Therapy of the American Medical Association for consideration of apparatus used in fever therapy was stated.<sup>102</sup>

[The choice of apparatus, provided it is safe and easily controllable, is of little concern; most important is the careful supervision of patients during treatment.—Ed.]

The physiologic effects of fever therapy as given in previous Reviews were again noted.<sup>51, 279, 594, 641</sup> Changes in the blood picture before and after fever therapy were noted by Krusen; a characteristic "febrile hemogram" was seen: a postfebrile leukocytosis, an increase of polymorphonuclears and nonfilamented cells, later of monocytes, lastly of lymphocytes. The effects of experimental fever on human circulation (cardiac output, velocity of blood flow, blood volume) were studied (Moore and Kinsman).

*Indications and contraindications* for fever therapy were noted and were as given in previous Reviews.<sup>497, 564, 913, 614, 793</sup> Some described in detail the *management of patients during fever therapy*.<sup>29, 25, 26, 75, 217, 497, 564, 597, 622, 641</sup> To combat or prevent symptoms of anoxemia and oxygen deficiency during prolonged hyperpyrexia, Roth recommended the routine use of oxygen and carbon dioxide, the latter easily provided by "dry ice." A method for the continuous registration of rectal temperatures during fever therapy was described.<sup>659</sup>

*Complications and Untoward Reactions.* The types, incidence and management of minor complications of fever therapy (herpes, burns, headache, gastrointestinal symptoms, tetany) were again reviewed.<sup>188, 217, 218, 279</sup> Stecher and Solomon noted their incidence during 1000 sessions of fever given to 204 patients. One group of 142 patients with acute or chronic non-gonorrheal arthritis, syphilis and various other diseases received 830 "mild treatments" (three to five hours at 103 to 105° F.). A second group of 62 patients with gonorrhea received 170 "severe treatments" (four to seven hours at 106 to 107° F.). The incidence of complications follows: nausea and vomiting accompanied 28 per cent of the mild, 36 per cent of the severe treatments. Burns accompanied 2 per cent of the mild, 14 per cent of the severe treatments. Herpes affected each group equally, 32 and 31 per cent of patients. However, anorexia and loss of weight were more common after mild than after severe treatments. Thus, anorexia accompanied 81 per cent of the mild, 65 per cent of the severe, treatments. Three patients in each group experienced the severe reaction of sudden uncontrolled

fever with mania, coma, circulatory collapse and shock—an incidence of 0.36 per cent of the mild treatments, 1.76 per cent of the severe treatments. There were no deaths but transient (10 days) right facial paralysis and aphasia affected one of the patients who received severe treatment.

Others noted serious complications, transient auricular fibrillation in two cases,<sup>217</sup> hematemesis in two cases,<sup>217</sup> heat collapse in three cases,<sup>551</sup> severe shock with recovery in six cases (but with death in two other cases).<sup>388</sup> Data on the major and fatal complications previously reported were reviewed by Humiston.

Eleven deaths related to fever therapy were reported during 1937 but this was in connection with many thousand sessions of fever. No deaths occurred during 1001 treatments of 189 gonorrheal patients of Potter, Redewill and Longley. Only one death occurred during about 2500 sessions of fever given by Parsons, White, Hardaway and Barnes; details of this death were not given. During 1500 treatments Epstein noted death of two severely parietic patients. Among 516 patients given 2580 treatments by Desjardins, Popp and Stuhler the mortality rate was 0.2 per cent: a girl with pelvic gonorrhea died after one session of fever. Warren, Scott and Carpenter treated 283 gonorrheal patients in six years with sessions of fever of varying lengths: only one death occurred, that of a young gonorrheal patient who died 26 hours after a long (24 hour) session of fever. Two additional deaths were reported by Wilbur and Stevens, two by Kopp and Solomon, one by Chunn and Kirkpatrick and one by Hartman. Findings at necropsy included the following: moderate dehydration of body tissues; cloudy swelling, early necrosis or parenchymatous degeneration of liver, vacuolar degeneration but no hemorrhages in adrenals; acute passive congestion of lungs with hemorrhages, softening of spleen, tubular or parenchymatous degeneration of kidneys, petechial hemorrhages of epicardium, myocardium, endocardium and kidneys; edema and hyperemia of intestines; subdural hemorrhages with cerebral necrosis, edema, congestion and cellular degeneration. To Wilbur and Stevens these findings markedly resembled those of fatal sunstroke. Kopp and Solomon considered the severe reactions of six patients who recovered and of two who died to represent true shock; its features were described. As a result of clinical and experimental studies of patients and animals Kopp and Solomon, and Hartman, regarded anoxemia as perhaps the chief cause of these complications; chief among the measures advocated for their prevention or control were administration of oxygen and carbon dioxide (e.g., by a nasal catheter), the avoidance of sodium amytal or adrenalin during sessions of fever. The use of caffeine was permitted by some<sup>388</sup> but condemned by others.<sup>703</sup>

#### CONCLUSIONS ON THE MERITS OF FEVER THERAPY FOR GONORRHEA AND GONORRHEAL ARTHRITIS

Serious or fatal complications are rarely encountered when fever therapy is applied by a trained personnel. Although the mortality rate therefrom



is less than 0.2 per cent, the realization that death occasionally may occur from almost any method of treatment affords no consolation for the loss of a patient.<sup>188</sup> As one writer<sup>116</sup> put it: Assuredly such a potent weapon as fever therapy is not warranted against "small game syndromes." Gonorrhea and its complications are not small game and it has been amply shown that against them fever therapy provides a potent weapon. In spite of this its disadvantages are apparent. Pelouze regarded it incapable of universal use, "beyond the reach of the masses." Some patients are physically and emotionally unable to accept it.<sup>111</sup> Parran concluded, "While pyretotherapy may be effective in ordinary acute gonorrheal arthritis I believe that those who advocate its routine application for all such patients are inexperienced theorists. The incidence of acute gonorrhea is much too high and the technique of fever induction much too complex, costly and dangerous for general routine use."

[In the light of the results obtained from the use of sulfanilamide in cases of gonorrhea and its complications it would appear that fever therapy may be largely supplanted. In evaluating fever therapy it should be remembered that the work herein and heretofore reported was mostly done before sulfanilamide was available. Even though fever therapy may soon become outmoded, no one should discount the extremely valuable, highly scientific and courageous pioneer work of those who collaborated in its development. Although it is admittedly an heroic form of treatment, in its time it has constituted the greatest advance ever made in the treatment of gonorrhea and of certain other diseases as well. Nor should it be too hastily discarded; further comments will be made on the possible future rôle of artificial fever in treatment.—Ed.]

#### SULFANILAMIDE: ITS DEVELOPMENT AND ITS USE IN GONORRHEA

The medical year 1937 might well be tagged "sulfanilamide year" for although the chemical, pharmacologic and experimental clinical background for use of the preparation had been well laid in the preceding five and more years, 1937 first brought wide clinical recognition. Seldom has any new drug aroused so much enthusiasm or so rapidly gained attention. "Much of this enthusiasm is warranted. The drug is truly remarkable." "Reports of its use are literally amazing. If the test of time bears out these early promises it will rank among the great therapeutic advances." So ran editorials in cautious medical journals.<sup>204, 207</sup> The development of sulfanilamide has a greater significance than many realize.<sup>184, 420</sup> Heretofore specific chemicals have been found for use only in nonbacterial diseases, those caused by protozoa (quinine and atebine in malaria, arsphenamine, mercury and bismuth in syphilis; trypanosamid in trypanosomiasis, thymol and carbon tetrachloride for intestinal parasites). Until now no chemical specific has been developed for use in bacterial diseases (since optochin for pneumococci and chaulmoogra oil for leprosy have not yet gained clinical recognition as specifics). But the advent of sulfanilamide has established beyond all doubt that effective chemotherapy of microbial diseases is attainable. Because of this a brief outline of the development of sulfanila-

mide, as given by Hoerlein, Long,<sup>420</sup> Long and Bliss,<sup>424</sup> Welch and others, seems appropriate.

*Discovery and Development.* This will be given in summary:

- 1908. First description of para-amino-phenyl-sulfonamide—Gelmo.
- 1909–1910. Incorporation of sulfonamide grouping in azo dyes—Hörlein, Dressel and Kothe.
- 1913. Discovery of bactericidal properties (in vitro) of certain azo dyes—Eisenberg.
- 1919. Further work on bactericidal properties of azo compounds, including para-amino-phenyl-sulfonamide—Heidelberger and Jacobs.
- 1920. Existence of the dye compound later to be called prontosil was postulated by Bayer Company and Interessen Gesellschaft Farbindustrie.
- 1932. Prontosil synthesized by Mietzsch and Klarer, patented Christmas Day. Domagk, Director of the experimental pathological laboratory at Elberfeld, studied effects of prontosil on hemolytic streptococcal infections in animals; results seemed "too good to be true," hence he delayed publication until 1935. Meanwhile clinical reports began to appear.
- 1933. First clinical report: effect of prontosil ("streptozon") on staphylococcal sepsis—Foerster.
- 1934. Reports by Grutz: good effects of prontosil (oral) and "prontosil solution" (intravenous) in erythemas.  
Veil noted beneficial effects of prontosil solution in "rheumatism."
- 1935. Good results from prontosil and prontosil solution in erysipelas—Gmelin.  
First report (Domagk) of results of prontosil on experimental hemolytic streptococcal infections in animals.  
Further German reports on the clinical effects of the prontosils on hemolytic streptococcal infections—erysipelas, puerperal fever, meningitis and certain other diseases including "infectious arthritis" (Klee and Römer, Schreuss, Anselm, Gantenberg, Imhauser, Bingold, Einhauser, Fuge, Roth, Schranz, Riecke, Scherber, Püschel); also on pneumococcal and staphylococcal infections (Recknagel).  
French reports on effects in experimental diseases in animals—Levaditi and Vaisman; Nitti and Bovet.  
Identification of colorless para-amino-benzene-sulfonamide as active agent in the dye compound prontosil by the Tréfouëls, Nitti and Bovet.  
Favorable effects in gonorrhea—Schreuss.
- 1936. First French clinical report (Vermelin and Hartemann): use of "Rubiazol" (prontosil) in puerperal sepsis; oral preparation safe; intravenous preparation toxic.  
Further French clinical reports on erysipelas and puerperal infections: Floch; Lemierre, La Porte, Laudat and Daum; Meyer-Heine and Huguenin; Bloch-Michel, Conte and Durel.  
First English reports on the effects of the prontosils on experimental and clinical streptococcal and meningococcal infections—Colebrook and Kenny; Buttle, Gray and Stephenson.  
Clinical and experimental work of Kramer, Hörlein, and Domagk.  
Recognition of occasional serious toxicity—Colebrook and Kenny; Colebrook, Buttle and O'Meara.  
Further studies on effects of prontosil in gonorrhea—Linser; Haugk.
- 1937. First and subsequent American reports by Long and Bliss on the effect of sulfanilamide on experimental and human beta hemolytic streptococcal infection.

Effect on pneumococcic infections: experimental (Rosenthal; Cooper, Gross and Mellon; Long and Bliss; Rosenthal, Bauer and Branham) and human (Heintzelman, Hadley and Mellon; Long and Bliss).

Effect on meningococcic infections: experimental (Proom; Proom and Buttle) and human (Schwentker, Gelman and Long; Long and Bliss).

Effect on experimental typhoid and paratyphoid B infections in mice—Buttle et al.

Effect on gonococcic infections: Grutz; Dees and Colston, Rueter and others. Further results in various beta hemolytic streptococcal infections; puerperal sepsis (Foulis and Barr), scarlet fever (Peters and Havard), streptococcal meningitis (Gray; Causse, Loiseau and Gisselbrecht; Arnold; Schwentker et al.; Anderson; Weinberg, Mellon and Shinn, Douthwaite and others.)

Development of tests for quantitative determination of sulfanilamide in body fluids and studies on its absorption and excretion—Marshall, Emerson and Cutting.

Recognition of varied toxic reactions from sulfanilamide.

Further standardization of preparations and official approval of the term "sulfanilamide."

*Preparations.* The literature contains a confusing number of chemical and trade names for the various sulfonamide compounds. Some preparations, made for investigative purposes and described by full, not simplified, chemical terms have already been discarded as being more toxic or less effective than others. This discussion chiefly concerns the three main compounds used, to which many names have been given (table 1).

1. The first compound, made by Mietzsch and Klarer and used by Domagk, was a diazo dye, variously described as yellow, orange, red, brick red, or yellowish-red. It was 4-sulfamido-2':4-diaminoazobenzene, called "prontosil." It was first prepared in the form of a hydrochloride and was sparingly soluble. Later prepared as a base, it was completely insoluble in water. The red tablets were marketed as "prontosil," "streptozon," "rubiazol," "prontosil flavum" or "original prontosil." This preparation is no longer being promoted as later preparations were superior.

2. The next compound used was a prontosil solution, a soluble red azo dye for subcutaneous (not intravenous) injections. Neutral and easily soluble in water, it was the disodium salt of 4'-sulfonaminophenyl azo-1-hydroxy-7-acetyl amino-naphthalene-3:6-disulfonic acid. It was called "prontosil solution," "prontosil soluble," "red prontosil" or "prontosil rubrum," and streptozon S. Unfortunately this form and not "original prontosil" was marketed in the United States under the term "prontosil" (Winthrop); this led to confusion and some called it "prontosil (American)" to distinguish it from "prontosil (European)." "Prontosil soluble" had the disadvantage of staining tissues somewhat red.

3. The Tréfouëls, Nitti and Bovet (1935) noted that prontosil and prontosil solution, though different in structure, had the same antibacterial action and each possessed the sulfonamide group attached to the azo group in the para position. Compounds with the sulfonamide group in the ortho or meta position were not potent. Therefore the antiseptic activity was

TABLE I  
Sulfonamide Compounds

Original name	1. Prontosil (yellow or yellow red dye)	2. Prontosil solution (red dye)	3. Various names (white powder)	Some later compounds
Chemical name	4 sulfamido 2', 4' diamino azo ben- zene dihydro- chloride	4 sulfamido-ben- zene 2' azo, 1' hydroxy 7' acetylamino- naphthalene 3' 6' disodium sul- fonate	para amino- phenyl sulfon- amide or para amino benzyl sulfonamide	4—"Disseptal A": dimethylated di- sulfanilamide 5—"Disseptal B": monomethylated di-sulfanilamide 6—"Disseptal C": ("Di-sulfanila- mide"; Disulon) a nonmethylated amide; para- amino benzene sulfonyl-para- aminobenzene sulfonamide
Approved name (nonproprie- tary)			Sulfanilamide	7—"Proseptasine" or "Setazine": para-benzyl amino benzene sulphonamide 8—"Soluseptasine": disodium para (gamma- phenyl-propyl- amino) benzene sulphonamide- alpha-gamma disulphonate.
Synonyms or proprietary names	European prontosil Prontosil Prontosil I Original prontosil Prontosil flavum Rubiazol (4 differ- ent compounds) Streptozon Preparation 5214 (early European) Sulfamido-chrys- oidine (French)	American prontosil Prontosil soluble Prontosil II Red prontosil Prontosil rubrum Prontosil S Prontosil (Winthrop) Streptozon S	Prontosil album (Bayer) Prontylin (Winthrop) P.A.B.S. (Hewlett) Stramid (Alba) Streptocide (Evans Sons Lescher & Webb) Colsulanyde (Crookes) Sulfamidyl (Abbott) Sulphonamid P (Burroughs Wellcome) (Allen & Han- bury) (British Drug House) Sulphanilamide (Boots) Sulfanilamide (Squibb) Deseptyl (Hungarian) 1162 F (French)	

apparently due to the para position of the sulfonamide group; that is, the azo linkage was unnecessary, the active principle being para-amino-phenyl-sulfonamide itself. This simplified compound was more soluble, less toxic and more effective than its more complicated predecessors. Para-amino-phenyl sulfonamide is also known as para-amino-benzyl sulfonamide or para amino sulfamido benzene. Various proprietary names were given to it: P.A.B.S., the initials of its chemical name (Hewlett); stramid (Alba Chemical Co.); prontylin (Winthrop); streptocide (Evans Sons Lescher and Webb); colsulanyde (Crookes); prontosil album (Bayer); sulfamidyl (Abbott); sulphonamid P (Burroughs Wellcome; Allen and Hanbury; British Drug House); sulphanilamide (Boots) and sulfanilamide (Squibb).

The British spell it with "ph," Americans with "f." Since it is the amide of sulfanilic acid the American Medical Association approved the nonproprietary term "sulfanilamide" which is now in general use.<sup>112, 150, 157</sup> Numerous manufacturers prepare it in 0.3 gm. (5 grains) or 0.5 gm. (7½ grains) tablets or in powder form (white crystalline substance) to be dissolved for parenteral injections. Since Marshall, Emerson and Cutting found that preparations injected subcutaneously do not produce concentrations in blood higher than oral preparations, hypodermic use of sulfanilamide seems to have little place except when its oral use is not practicable (patients in delirium or coma).

In summary, prontosil and prontosil soluble are not sulfanilamide but compounds which apparently break down in the body to liberate (rather small amounts of) sulfanilamide, their active principle. Now this active principle is used alone and in larger, more effective doses than are contained in prontosil or prontosil soluble.

Among numerous newer compounds synthesized to find preparations even more effective and less toxic are di-sulfanilamide (disseptal C or para-aminobenzene sulfonyl para-aminobenzene sulfonamide),<sup>700</sup> proseptasine, a benzyl derivative of sulfanilamide (para-benzyl aminobenzene sulphonamide), and soluseptasine or disodium-p-(gamma-phenyl-propyl-amino) benzene sulphonamide-alpha-gamma-disulphonate.<sup>239</sup>

In animals with experimental beta hemolytic streptococcal infections Barlow found sulfanilamide (prontylin) more effective than prontosil and he found disulon (or disulfanilamide) superior to sulfanilamide. Similarly Whitby found proseptasine much less toxic than sulfanilamide but equally effective. Soluseptasine (an injectable preparation) was less toxic than prontosil soluble but equally effective. Sulfanilamide was effective against experimental meningococcal infections but proseptasine and soluseptasine were not. Two experimental diaminobenzenesulfonanilide compounds possessed polyvalent action: one against streptococcus, pneumococcus and meningococcus, the other against streptococcus and pneumococcus.

[Such rapid advances are being made in the preparation and use of these related compounds that some of these data may be out of date when published. Therefore readers are obliged to consult the latest (1938) references on the value of newer preparations and the doses currently recommended.<sup>58, 465</sup>—Ed.]

*Mode of Action.* The original prontosil had only a slight antistreptococcal action in vitro but a strong effect in vivo (Domagk, 1935). Also prontosil solution had little effect in vitro but was potent in vivo (Colebrook and Kenny, 1936; Long and Bliss<sup>422</sup>). But sulfanilamide in a concentration of 1:10,000 was definitely bactericidal and bacteriostatic against certain bacteria in vitro as well as in vivo (Colebrook and Kenny, 1936; Colebrook, Buttle and O'Meara, 1936; Long and Bliss<sup>421, 422</sup>). Prontosil and prontosil solution were reduced in the body to form sulfanilamide. Perhaps prontosil and prontosil solution were, per se, relatively inert and effective only in relation to their quantitative reduction to sulfanilamide (Tréfouël, Nitti and Bovet, 1935; Colebrook, Buttle and O'Meara, 1936). This explanation,

however, does not satisfy those (e.g., Hoerlein) who have noted good results from sulfonamide compounds (e.g., disseptal C) which cannot be reduced to sulfanilamide in vivo, nor those who have obtained excellent results from amounts of prontosil solution which liberate only a few grains of sulfanilamide a day (Brown, Bannick and Habein). Perhaps sulfanilamide is not the main or only effective agent in these compounds.<sup>79, 321</sup> The mode of action of prontosil and prontosil solution is thus not yet known.

The mode of action of sulfanilamide is also obscure. Some (Levaditi and Vaisman 1935, 1936) suggested that it has a true bactericidal (antiseptic) action in vivo by preventing the capsule formation of streptococci, thus favoring natural phagocytosis. Some found no evidence of increased phagocytosis in animals treated with sulfanilamide.<sup>709</sup> Long and Bliss,<sup>50, 421, 422</sup> finding no evidence of any antiseptic effect of sulfanilamide in vitro (in the sense that phenol has), concluded that an effect other than bacteriostasis alone was involved; sulfanilamide inhibits growth of certain bacteria and injures them so that they can be markedly phagocytosed by leukocytes. Those interested further in theoretical discussions on the mode of action of sulfanilamide are referred to the reports of Bliss and Long, Mellon and Bambas, and Barron and Jacobs.

*Absorption, Diffusion and Excretion of Sulfanilamide.* Developing a method to determine concentrations of sulfanilamide in tissues and fluids Marshall, Emerson and Cutting studied its diffusion. Although the rate varies somewhat in different persons, absorption from the gastrointestinal tract is rapid and generally complete in about four hours. The drug then diffuses readily from blood to all body tissues and fluids where it is almost evenly distributed, concentrations in saliva, pancreatic juice and cerebrospinal fluid being only slightly less than that of blood. It takes two to three days to establish equilibrium between the amount ingested and the amount excreted; when administration of the drug is stopped, it takes two to three more days to free the system of it. By giving doses every four hours, concentrations in blood between 1:5000 and 1:10,000 can be readily attained and maintained as well by the oral as by the subcutaneous route. Therefore oral administration is preferable. Excretion is rapid and almost wholly via the kidneys, appearing in urine of man in a free and in a conjugated (acetylated), almost inactive form. Patients with impaired kidneys excrete it more slowly, therefore high concentrations in blood can be more rapidly attained. In such cases the drug must be administered with special care. According to Hill<sup>317</sup> the urine of patients excreting sulfanilamide has no bactericidal activity against beta hemolytic streptococci. But Helmholz and Osterberg and Cook and Buchtel noted that administration of sulfanilamide produces urine strongly bactericidal for the usual bacteria causing urinary tract infections except *Streptococcus faecalis*.

*Pharmacology.* The effects on animals were studied by Marshall, Emerson and Cutting, by Hawking, and by Hageman. Six grams of sulfanilamide per kilogram killed all, and 4 gm. per kilogram killed half, the mice tested. One gram per kilogram given to dogs produced nausea, vomiting, diarrhea, hyperpnea and neurologic symptoms resembling those of a decorticated dog. Sulfanilamide has almost no action on smooth muscle, heart or blood pressure. Animals which survived large doses showed no changes in liver, kidneys or other viscera. Animals which died from the drug had degenerative changes in the central nervous system. These facts hardly apply to human beings for lesions were produced in animals only by extremely large doses.

*Toxicity of Sulfonamide Compounds.* In general sulfanilamide and related compounds are either nontoxic or only mildly toxic. Toxicity affects ambulatory patients oftener than those in bed.<sup>80, 410, 422, 424</sup> Mild toxicity affects 50 per cent or more patients<sup>335</sup> being treated, producing malaise, tinnitus, dizziness, drowsiness, lassitude, anorexia, weakness, slight headache.<sup>78, 79, 80, 410</sup> In the presence of mild toxicity the same dose may be continued, or it may be reduced if the patient is not relieved by rest in bed.

Moderate toxicity produces the foregoing symptoms plus cyanosis (with or without sulfhemoglobinemia or methemoglobinemia), numbness and tingling of hands, face or feet, skin rashes, abdominal pain, diarrhea, fever, acidosis or a toxemia resembling that of ethyl alcohol. In such cases the dose should be reduced or administration stopped, or one may invite disaster.<sup>79, 80</sup> Signs of severe toxemia are collapse, fever, rapid pulse; leukopenia or agranulocytosis; hemolytic crises; jaundice. In such cases administration must be stopped and fluids forced. Sulfanilamide is soluble in water and readily excreted in urine. In acute toxicity, Long<sup>410</sup> sometimes prescribed 5000 c.c. water (oral) within 6 hours. Blood transfusions may be required in leukopenia or hemolytic crises.

In summary, sulfonamide compounds are relatively nontoxic for man although a serious reaction occasionally occurs. Among the 4000 reported patients so treated only 10 deaths, apparently related to the drug, have occurred (Mellon, Gross and Cooper); in five of them the drug may not have been the actual cause of death. There was apparently no correlation between the deaths and the dose used.

*Sulfanilamide Fever.* Rise in temperature (generally 101 to 104° F.; occasionally higher), may appear between the third and tenth day of treatment with repeated small doses or within 24 hours after a large dose.<sup>135, 410, 421, 422, 609</sup> If it occurs, use of the drug should be stopped for two to three days and the fever will disappear promptly. This fever must be distinguished from that of the primary disease. It may occur from one to five days after administration is stopped. Fever, with or without rash, affected 16 per cent of 134 patients of Hageman and Blake.

*Gastrointestinal Symptoms.* Nausea and vomiting not infrequently arise, sometimes with fever or intense headache,<sup>815, 713</sup> in one case with unconsciousness.<sup>167</sup>

*Renal Symptoms.* Generally these were not noted, although some considered irritability of the urinary tract common (Colebrook and Kenny 1936, Foulis and Barr). One of Reuter's patients noted marked slowing and weakness of urination.

*Nervous System.* This may be involved in animals receiving toxic doses but no comparable symptoms in man were reported, though Whitby had heard of one such case. Cokkinis noted loss of memory, deafness and headache once, loss of taste for tobacco and alcohol once. Mild choreiform twitches affected an eight year old child.<sup>630</sup> One patient developed vertigo, nausea, dyspnea and loss of consciousness.<sup>251</sup> A patient of Bucy experienced severe reduction of vision and optic neuritis after taking 1 tablet of 5 grains (third course). [One of us, W. B., has encountered loss of memory, confusion, euphoria, loss of time sense.—Ed.]

*Skin Rashes.* These (with or without fever and sometimes severe enough for hospitalization) were frequently noted.<sup>83, 236, 246, 261, 284, 285, 315, 335, 410, 460, 475, 490, 496, 513, 594, 601, 602</sup> The rash was generally morbilliform or maculopapular, occasionally vesicular, erythro-edematous, hemorrhagic, urticarial or like erythema multiforme.

It generally appeared on face, trunk and extremities after 5 to 14 days of treatment. It affected 60 per cent of Schwentker and Gelman's cases. Once it appeared after the ingestion of 1 tablet of 5 grains.<sup>601</sup> If the rash is mild, treatment may be continued or the dose reduced. Rash and fever disappear within 48 to 72 hours after administration is stopped.<sup>419</sup> Salvin noted one case of diffuse urticaria, sneezing, lacrimation and dyspnea. Myers, Vonder Heide and Balcerski noted severe exfoliative dermatitis, edema, purpura, fever, marked leukocytosis and eosinophilia, acidosis and transient jaundice in a gonorrheal patient given 1325 grains (88.3 gm.) of sulfanilamide in 28 days.

In some cases the factor of photosensitivity was noted, lesions appearing only on parts exposed to sun. The lesions were urticarial, erythematous, macular, maculopapular or vesicular.<sup>83, 469, 496, 513</sup> Brunsting noted excess porphyrinuria in two such cases. Patients taking the drug should avoid undue exposure to sun.

*Acidosis.* Most patients develop a fall (average 14.1 volumes per cent) in the  $\text{CO}_2$  combining power of blood; a few develop clinical acidosis—air hunger without ketonuria.<sup>419, 424, 640</sup> The cause of the phenomenon is not clear but there is an increased urinary excretion of sodium and potassium. Intravenous or subcutaneous injections of  $\frac{1}{6}$  molar sodium lactate solution will correct it.<sup>38, 424</sup> To prevent it 10 grains of sodium bicarbonate are given with each dose of sulfanilamide by some physicians.

[In view of more recent work the question of the production or prevention of acidosis should be considered unsettled. Some doubt that such small doses of alkali are effective. Indeed some now regard the use of alkalis contraindicated.—Ed.]

*Leukopenia.* This was occasionally noted with depression of myeloid elements.<sup>424, 530</sup> Since sulfanilamide contains the benzene ring it may affect the hematopoietic system.

*Acute Hemolytic Anemia.* This, frequently with jaundice, was noted in 15 cases.<sup>299, 347, 386, 424, 705</sup> It was nonfatal but transfusions were often necessary. Its mechanism is unknown. Estimations of hemoglobin and differential blood counts should be made every two to three days to obtain forewarning of hemolytic anemia. If the hemoglobin or erythrocyte counts are notably reduced, administration of the drug should be continued only with great caution.<sup>420</sup> Jaundice may accompany toxic hemolytic anemia or agranulocytosis.

*Agranulocytosis.* This was noted 10 times; it was fatal in 7 cases.<sup>63, 194, 347, 424, 425, 459, 475, 547, 747</sup> It occurred after prontosil, prontosil solution, sulfanilamide and proseptasine. The mechanism of its production differs from that seen in the agranulocytosis due to amidopyrine.<sup>424</sup>

*Sulfhemoglobinemia and Methemoglobinemia.* These conditions may complicate sulfanilamide therapy. To the three cases of sulfhemoglobinemia earlier reported by Colebrook and Kenny (1936) can be added about 13 more cases,<sup>18, 135, 190, 244, 419, 527</sup> one of which was fatal.<sup>249</sup> Sulfhemoglobinemia was not noted among the 235 cases of Peters and Havard and Whitby. The condition may represent an idiosyncrasy as its appearance seemed unrelated to the dose used.<sup>249</sup> Although it may occur in patients to whom sulfates have not been given<sup>419, 422, 527</sup> the latter supposedly predispose to it. Therefore, during and for two or three days before sulfanilamide therapy, patients should *not* be given magnesium sulfate dressings, magnesium sulfate or other related saline cathartics. One must also avoid licorice powder (or other drugs containing sulfates), the anthracene group of aperients, aniline dyes (phenacetin and acetanilid), phenylhydrazine derivatives, amidopyrine, sulfonal, methylsulfonal.<sup>190, 239, 709</sup> To prevent sulfhemoglobinemia Archer and Discombe also prescribed preliminary colonic enemas and, during treatment, the use of a low residue diet poor in sulfur, and 30 to 45 c.c. liquid paraffin daily. When sulfhemoglobinemia occurs cyanosis may be spectacular and alarming but not serious if use of the drug is stopped. One should not look only for cyanosis but should check the patient's hemoglobin every four days.<sup>190</sup>



After administration is stopped sulfhemoglobinemia may last six weeks; methemoglobinemia lasts only about 24 hours.<sup>527</sup> Previously noting sulfhemoglobinemia, Long and Bliss<sup>425</sup> later were uncertain of the accuracy of their spectrophotometric readings and were not sure whether true sulfhemoglobinemia really occurred.

[In patients receiving full doses of sulfanilamide cyanosis practically always appears in 8 to 12 hours after the initial dose and may be present for two to four days before met- or sulfhemoglobinemia can be detected. However the latter are rarely the causes of cyanosis in our experience; cyanosis is produced in some other manner.—Ed.]

Methemoglobinemia and cyanosis were noted in 50 per cent of Hageman's 60 patients on sulfanilamide. Seven other cases were noted.<sup>18, 46, 527, 662</sup> It occurred in patients who were receiving generally large doses of sulfanilamide,<sup>527</sup> but sometimes small doses.<sup>46</sup>

*Cyanosis.* Mild to marked cyanosis occurs in 75 to 90 per cent of patients using sulfanilamide.<sup>419, 425</sup> Cyanosis alone is no contraindication to continued treatment. It may occur with sulfhemoglobinemia or methemoglobinemia but before assigning the cause one must examine the blood spectrophotometrically. Slight cyanosis and tachypnea may arise with acidosis.<sup>422</sup> Archer and Discombe saw it due to coincident pneumonia, and to overdosage of paraldehyde. The cause of the cyanosis is not known; it is rarely due to sulfhemoglobinemia or methemoglobinemia, according to Marshall and Walzl but may be due to the presence of a black oxidation product of sulfanilamide which stains erythrocytes. Even in cases of deep cyanosis blood lactic acid was not significantly increased.<sup>38</sup>

It is widely known that the deaths from elixir of sulfanilamide—Massengill were due not to sulfanilamide but to the solvent used—diethylene glycol. Discussion of this tragic incident is unnecessary here.<sup>113, 114</sup>

*Sulfanilamide for Gonorrhea and Gonorrheal Arthritis.*—In the United States the effect of sulfanilamide on gonorrhea was first reported in May 1937 by Dees and Colston and by Reuter but in Germany previous work had been done. The beneficial effects of prontosil used alone or with orthodox remedies in males and females with gonorrhea had been noted by Schreuss (1935), Linser (1936) and Haugk (1936). Others (Ehlers 1936, Becker 1937) noted no results from prontosil. In May 1937 Dees and Colston treated 19 patients with gonorrhea (none with arthritis) most of whom received daily (in four divided doses) 4.8 gm. of sulfanilamide for two days, 3.6 gm. for three days and then 2.4 gm. for four to eight more days. In 12 cases urethral discharges stopped in one to three days and smears became negative in two to five days. A few cases were more resistant: "Three or four were little if any benefited." [Further experience indicates that these doses were inadequate for all cases.—Ed.] In May and November 1937 Reuter reported results from sulfanilamide in 100 cases of gonorrhea of all degrees and stages. Patients received 40 grains daily for apparently only three days. Rapid recovery resulted in 90 per cent of the 100 cases, generally within five days; in 93 per cent of the 40 acute cases, in 88 per cent of 60 chronic cases (over two weeks' duration). [It is interesting to note the percentage of cures among these patients given doses now considered inadequate.—Ed.] Side-effects of the drug were often noted; those who "complained early and bitterly" of them responded best; those who did not respond apparently tolerated the drug. Of the series none had

arthritis but in a new series (to be reported) was one case of gonorrheal arthritis which showed "astonishing improvement."

In December Colston, Dees and Harrill reported further experiences. Results were successful in all but 10 (16 per cent) of 62 cases of genito-urinary gonorrhea (none with arthritis). Sulfanilamide was given longer than previously and in a little greater dosage: first two days, 5.3 gm. (80 grains); next five days, 4.0 gm. (60 grains); next seven days, 2.7 gm. (40 grains); next 14 days, 1.3 gm. (20 grains) in each case daily. Recurrences occurred only when smaller doses were used or when treatment was prematurely stopped. Records of 10 patients with gonorrheal arthritis treated by colleagues were reviewed. The average duration of these cases was 19 days, excluding one case of two years' duration. Joint pains disappeared after an average of two days and joint swelling after an average of 13 days from the onset of sulfanilamide therapy. Buchtel and Cook, and Douthwaite each noted "dramatic recovery" in one case of gonorrheal polyarthritis. Among 250 patients with gonorrhea treated with sulfanilamide by Cokkinis were an unstated number with gonorrheal arthritis or fibrositis, most of whom "reacted quite well" (details not given). In most cases, uncomplicated acute and chronic urethritis cleared up rapidly and completely but in cases of acute prostatovesiculitis, with or without epididymitis, there often was great resistance to treatment. Many were given local treatment as well as sulfanilamide, the latter generally in doses of 3 to 5 gm. daily for two to seven days; thereafter, as necessary, 3 gm. daily for seven more days and 1.5 gm. daily for seven more days. "We now possess an effective remedy for gonorrhea and for most of its complications." Cokkinis recommended a total dose of not more than 60 to 70 gm. in three weeks.

Other reports noted the effect of sulfanilamide or related drugs in cases of gonorrhea without arthritis. Herrold noted results in 30 cases: in 10 (83 per cent) of 12 cases, chronic gonorrhea was cured in 7 to 21 days; but in only 1 (25 per cent) of 4 subacute cases and in only 4 (28 per cent) of 14 acute cases was a cure effected. Doses of sulfanilamide were small, however, generally 20 to 45, rarely 80, grains daily. The use of 30 to 40 grains of sulfanilamide daily proved "almost a specific" in most of Branham's (unnumbered) cases. The acute discharge was "invariably relieved" but the "spectacular" results led to a false sense of security as prostatitis often persisted when treatment was prematurely stopped. Of Buchtel and Cook's 31 patients, 27 (87 per cent) were promptly cured within one week, 4 had symptoms after one week of treatment. In those cured, recurrences were not noted in spite of repeated examinations. The general plan of dosage was 60 to 80 grains (4 to 5.3 gm.) daily for two days, then 40 grains (2.6 gm.) daily for about 10 days more. Even when clinical cure of gonorrhea was noted early, 20 grains (1.3 gm.) daily was given for 10 to 14 more days. This plan was not routine: some patients must start on a small dose and gradually increase it; others noted good results on a small daily dose; about 10 per cent of patients could not take the drug at all. To reduce symptoms of toxicity it was recommended that patients remain in bed the first two or three days of treatment.

Carey treated two patients with acute vulvovaginitis, with small doses of sulfanilamide (20 to 45 grains daily): One was cured; one was not. Anwyl-Davies treated 19 acute cases with small doses of sulfanilamide; results were "distinctly dis-

appointing"; later, 20 patients were treated with larger doses (4.8 gm. daily for two days, 3.6 gm. daily for three days, 2.4 gm. daily for four to eight days). Results were still "unsatisfactory"; the drug was considered "ineffective." These poor results were promptly challenged by others. Excellent results (not statistically analyzed) were noted by Erskine, Johnson and Lloyd in treatment with larger doses (those used by Dees and Colston) of 100 patients with gonorrhea. Treatment with prontosil soluble and sulfanilamide, combined with irrigations, proved rapidly effective in 90 of Crean's 100 cases of acute and chronic gonorrhea. Patients who did not respond within 18 days were not likely to respond at all. Thirty patients with gonorrhea were treated by older methods; it took three times as long to cure them as to cure patients treated with sulfanilamide.

Orr treated 134 patients: 91 (88 per cent) of 104 males and 26 (87 per cent) of 30 females were cured generally within one to five days, 25 patients within 5 to 15 days. Dosage of sulfanilamide was 80 grains daily for four days, 40 grains daily for four more days, 20 grains daily for seven more days. According to Brown, Bannick and Habein, at least 90 per cent of male patients and 80 per cent of female patients with gonorrhea "adequately treated" with sulfanilamide were cured. At first, 75 to 90 grains daily (in six divided doses) was given until a concentration of 8 to 10 mg. per cent was established. When definite improvement was noted the dose was reduced to 60 grains daily (given in four divided doses); with further improvement it was reduced to 50 grains daily and continued if necessary for three to four weeks. Among those cured was a woman previously unimproved by repeated fever therapy and prolonged local treatment. Of 72 patients treated by Watts, Oden and Gordon, 45 (63 per cent) were "cured" or "apparently cured"; 13 (18 per cent) were improved; 14 (19 per cent) were unimproved. Dosage was 80 grains daily for two days, 60 grains daily for three more days, 40 grains daily for nine more days.

Results were satisfactory in 88 per cent of Humiston's 100 cases, unsatisfactory in 12 per cent. Patients were given sulfanilamide, 45 grains daily for two days, 30 grains daily until gonococci were no longer found, and 15 grains daily until a provocative course was completed. The latter consisted of daily prostatic massage, instillation of silver nitrate and final injection of gonococcus vaccine: if gonococci were not found thereafter the patient was believed cured. A child with gonorrheal vulvovaginitis was cured by McCullough.

*Method of Administration.* Since results from sulfanilamide are dependent on its adequate concentration in blood, a rational and successful method of treatment is the administration of relatively large initial doses followed by smaller doses sufficient to maintain an adequate concentration of the drug in the blood (1:10,000 concentration = 10 mg. sulfanilamide per 100 c.c. blood). Long and Bliss<sup>419, 421, 424</sup> therefore recommended, during the first 24 hours, the oral use of 5 gm. sulfanilamide (or 1 gm. for every 20 lbs. or 9 kg. [i.e.  $\frac{3}{4}$  grain per pound] body weight) or 120 c.c. of prontosil soluble (2.5 per cent solution; 1 c.c. for each pound of body weight).

Their general plan of dosage follows:

1. Dosage of sulfanilamide orally for patients weighing over 100 lbs., a total dose of 50 to 80 grains in the first 24 hours, followed by a maintenance dose of 15 grains every 4 hours; for patients weighing 50 to 90 lbs., a dose of 30 to 50 grains in the first 24 hours and 10 to 15 grains every 4 hours thereafter; for children weighing 25 to 50 lbs., a dose of 20 to 30 grains during the first 24 hours and thereafter 5 to 10 grains every 4 hours.

Since patients absorb and excrete the drug variably, doses may vary and they are controlled by estimating the concentration of sulfanilamide in the blood by the method of Marshall, Emerson and Cutting, 4 hours and 24 hours after the initial dose.

2. Dosage of parenteral sulfanilamide solution. Doses follow: For persons over 100 lbs. in weight an initial hypodermoclysis of 500 c.c. of a 1 per cent solution, thereafter two doses of 300 c.c. each at 8 hour intervals; for persons weighing 50 to 90 lbs. an initial dose of 200 to 400 c.c. followed by 200 c.c. at 8 hour intervals; for children weighing 25 to 50 lbs., an initial dose of 100 to 300 c.c. followed by 100 to 200 c.c. at 8 hour intervals. Babies should receive a total of about 1 gm. of sulfanilamide per 10 lbs. of body weight during the first 24 hours. The simple method of preparing sulfanilamide powder for parenteral injection was given<sup>157, 424</sup>: Dissolve the sulfanilamide powder in sterile physiologic saline solution (0.8 to 1 gm. sulfanilamide to each 100 c.c. saline solution). Heat to 90° C. until solution accomplished; then cool to 37° C. and inject at that temperature. If it cools below 37° C. the drug will crystallize out.

3. Dosage of prontosil solution (parenteral). Directions follow: For persons over 100 lbs., 20 c.c. at four hour intervals (six injections the first 24 hours); for persons weighing 50 to 90 lbs., 10 to 15 c.c. every four hours; for children weighing 10 to 50 pounds, 5 to 10 c.c. every four hours until a definite clinical effect is noted; then the dose should be gradually decreased.

Since, theoretically, 100 c.c. of prontosil soluble (2.5 per cent solution) yields only 0.73 gm. of sulfanilamide, a great disproportion in the recommended amounts of these two drugs is obvious.

4. Summary. Of those who treated gonorrhea and gonorrheal arthritis as noted, several used doses approximating those recommended by Long and Bliss; others used smaller doses, in general with less success. With experience, the tendency was to use larger and more effective doses. The exact value of the drug in gonorrhea will not be determined until physicians have studied more patients treated by full doses so that adequate concentrations were attained and maintained.

[To attain rapidly and maintain an adequate concentration of sulfanilamide one of us, W. B., has adopted the following plan of dosage: (1) a daily dose of  $\frac{3}{4}$  grain sulfanilamide per pound body weight; (2) on the first day, large single doses to attain proper concentration rapidly; an initial dose equal to the total calculated dose for one day, or half as large a dose at the initial dose and a similar dose four hours later; (3) thereafter, to maintain a constant blood level give  $\frac{1}{6}$  the full calculated dose every four hours *day and night*; (4) fluid intake should be constant to maintain a constant blood level. *Example*: For a man weighing 160 lbs. the full daily dose of sulfanilamide would be 120 grains. The initial dose would be 120 grains (or 60 grains and another 60 grains in 4 hours); thereafter grains 20 every 4 hours day and night.—Ed.]

To prevent or anticipate significant toxicity the following were recommended: Instruct patients to avoid excess exposure to sun. Avoid sulfur containing compresses or drugs. Estimate the hemoglobin concentration and differential blood count every 2 to 3 days. Give 10 grains of sodium bicarbonate with each dose of sulfanilamide; this may help prevent gastric symptoms. Keep the patient in bed at least the first two to three days of treatment. In the presence of renal insufficiency test the concentration of blood sulfanilamide daily and stop administration if the concentration reaches 15 to 20 mg. per cent. With signs of minor toxicity force fluids; use of the

drug may not necessarily have to be stopped; the dose often can be continued or lowered. If patients are doing well, do not discontinue use of the drug prematurely. When major toxicity is apparent or feared, administration should be stopped at once and fluids forced.

[More recently patients have been treated with concentrations as high as 40 mg. per 100 c.c. blood. Only under special conditions should fluids be forced; this would lower the blood concentrations.—Ed.]

Obviously, sulfanilamide is most useful but occasionally is dangerous, and should be used only under a physician's supervision. On prescriptions should be written: "Do not refill."<sup>609</sup> In too many stores laymen can purchase the drug freely over the counter and a salesman may recommend the dosage. In such cases untoward effects will too often occur; steps must be taken to prevent misapplication of the drug.

*Sulfanilamide Combined with Fever Therapy.* Because of its toxicity, sulfanilamide cannot be taken in effective amounts by some patients; others may be infected with strains of gonococci unusually resistant to sulfanilamide. Therefore sulfanilamide will fail to cure a certain percentage of patients (10 to 15 per cent according to Buchtel and Cook). In some of the latter cases sulfanilamide, combined with fever therapy, may be effective. Results of this combination were successful in treatment of all of 10 patients who were resistant to sulfanilamide or to fever therapy alone, given by Ballenger, Elder and McDonald, who concluded that the remedies together were more effective than either alone. Sessions of fever of only 3 to 4 hours at only 103 to 104° F. were reputedly sufficient. Their plan of treatment had not yet been standardized and was not clearly stated. Eighty grains (5.3 gm.) of sulfanilamide were given daily for one or two days; a session of fever was given the next day, with 60 grains of sulfanilamide that day, and 60 or 80 grains the day after the fever. Use of the drug was then continued (60 grains daily) while two more sessions of fever were given, one every other day. Some patients were cured by only two or three days of sulfanilamide and one session of fever; others required three or four sessions of fever and several days of administration of the drug. This treatment may be indicated not only in resistant cases but for patients who urgently need an immediate cure for domestic or economic reasons.

Sulfanilamide plus fever therapy was also used by Cheetham and Roemer in treatment of 12 patients resistant to the drug alone: all were cured within 10 days. The program was that of Ballenger, Elder and McDonald except that the drug was administered (40 grains daily) for a total of 14 days. There were no recurrences.

[Three of us, W. B., M. H. D., and P. S. H., have also noted successes with this combination in the presence of resistance to the drug alone. But the combination is not always successful. Before considering results from the drug alone to be a failure, one must be sure that the "failure" is not due simply to an inadequate concentration of blood sulfanilamide from insufficient dosage or failure to keep fluid intake constant. The combined method seems indicated primarily if the disease is

truly resistant to full doses of the drug or if patients are tolerant of only small doses. —Ed.]

*Older Forms of Treatment.* In view of recent developments, the "older methods" seem outmoded but some will wish to compare their effects as controls on newer methods. Massive doses of gonococcus vaccine given subcutaneously were considered by Drummond effective in 28 cases of gonorrhea with and without arthritis. "Major shock," including fever (103 to 104° F.) was produced. Urethral discharge lasted (after treatment was begun) 3 to 14 days in the vaccine-treated group, 43 to 240 days in 14 controls treated by other methods. Specific antigonococcal serum therapy was "not very successful": Keefer and Spink were able to increase the bacteriolytic titer of serum thereby and clear the blood in some cases of bacteremia, but intra-articular injections of serum were ineffective. Goldey considered autoserotherapy advantageous. [We cannot agree.—Ed.] Anwyl-Davies treated 157 male patients, including 31 with arthritis, with a specific antitoxin or gonococcal filtrate. Results were "excellent" in 49 per cent, "good" in 30 per cent, "fair" in 15 per cent, "bad" in 6 per cent. Acute arthritis often was notably improved in a week; chronic arthritis within two to three weeks, but local genital lesions took 4 to 12 weeks to heal. The Corbus-Ferry filtrate seemed to Wishengrad of no value in acute gonorrheal urethritis, of possible value in chronic cases. Only 12 of Whitehouse's 30 patients were "cured" with this filtrate. Use of a bacteriophage or gonococcal (and mixed bacterial) lysate called "Neisso-jel" (Lilly) was condemned as dangerous by Brunet and Salberg. Robinson treated an unstated number of patients with gonorrheal arthritis with intramuscular injections of chaulmoogra oil; "excellent results were obtained in every case." Among patients treated with gold by Hartfall, Garland and Goldie were six with gonorrheal arthritis: one was "cured," two markedly improved. No conclusions were drawn.

Roentgenotherapy for gonorrheal arthritis was strongly recommended by Kahlmeter. However, results of treatment in 100 cases were not statistically analyzed: "At least 90 per cent of patients recover completely provided they come for treatment sufficiently early." Apparently Kahlmeter frequently used fever therapy also, considering the combination superior to fever therapy alone. [We have not been impressed with the results of roentgenotherapy in a small group of cases of gonorrheal arthritis.—Ed.] After aspiration of gonorrheal joints, the instillation of air "to distend joint surfaces, relieve pain, and aid in preventing deformities" was advised by Bohlman and Rombold. [One of us, A. J. K., has used this without success.—Ed.]

There appeared a number of reports on the standardization of older methods of treatment of gonorrhea of males and of females.<sup>42, 67, 144, 182, 192, 228, 444, 471, 478, 488, 493, 536, 537, 538, 560, 568, 711, 727, 732, 733, 734</sup> Marshall discussed the incidence and treatment (by old methods) of gonorrhea in pregnancy. Elliott treatments are contraindicated in acute cases but may be helpful in chronic cases of pelvic gonorrhea for which fever therapy may be imprac-

ticable; of 45 patients so treated by Randall and Krusen, 55 per cent were cured, 22 per cent improved.

The next few papers are reviewed, not because of their therapeutic value but because they describe certain interesting physiologic observations which, in spite of more dramatic current discoveries, may still be of more than academic interest.

Gonorrheal vaginitis of children is common and may occur at any age from birth to puberty; however, it is rare during the first few weeks of life and rare among adults. During the first five weeks of infancy, and again from puberty to the menopause, the vaginal epithelium is thick (30 to 40 layers of cells) and rich in glycogen, and the vagina is decidedly acid in reaction. From the fifth week of life until puberty the vaginal epithelium is thin (6 to 12 cell layers deep) and less rich in glycogen, and the vagina is alkaline (pH 7.0 to 8.0). Bumm (1885) observed that gonococci cannot invade intact squamous epithelium but have a distinct predilection for columnar epithelium; only the latter type of epithelium succumbs to gonococcal invasion. Gonococci do not attack the acid adult vaginal epithelium and are rarely found in vaginas of infants under three to five weeks of age. The blood of newborn children is rich in estrogen (acquired from the maternal circulation during pregnancy) for a short time only, then this substance rapidly decreases in amount. Perhaps newborn infants are protected from gonorrheal vaginitis because their blood is rich in estrogen and their vaginal epithelium is thick as in adults (Allen and Diddle, 1935). Allen (1928), Lewis (1933) and others noted that a thick-celled postnatal or adult type of vaginal epithelium (with acid vaginal reaction) could be induced in children by theelin (estrin, amniotin) when given hypodermically or in vaginal suppositories, but not when given orally. Lewis (1933) and others therefore administered estrogenic substances in cases of juvenile gonorrheal vaginitis in order to induce a metaplasia of vaginal mucosa which might be antigenococcal. Considerable success was attained although recurrences were frequent.<sup>47, 49, 186</sup>

Berry's results with theelin in 25 cases of juvenile gonorrheal vaginitis (15 acute, 10 chronic) were: cure in 68 per cent, temporary control in 28 per cent (recurrences later), failure in 4 per cent. In acute cases an average of 12,000 international units were given in an average of 56 days; in chronic cases, a total average of 8500 international units over an average of 34 days. The recommended dose was 1000 international units of theelin triweekly until the patient was symptomatically and bacteriologically cured. Sacher obtained good results from amniotin vaginal suppositories: one each night for three weeks, then one twice a week for three weeks.

Injections of estrin (1000 to 2000 international units) will also effect epithelial hyperplasia and metaplasia in the urogenital tract of male monkeys (Van Wagenen 1935; Deming, Jenkins and Van Wagenen). Hence estrin therapy might be of value also in gonorrheal urethritis of males. Intragluteal injections were given every one or two days. No results were noted in 12 patients given 2000 to 4000 international units within 20 days, or in 3 patients given 48,000 to 86,000 units in 13 to 16 days. Two patients given 88,000 and 92,000 units within 17 days were cured, within 10 days, of admittedly "slight" urethritis.

Recently Hall and Lewis (1936) and Karnacky (1936) concluded that the histologic changes of vaginal epithelium were not directly but indirectly responsible for gonococcal destruction. When theelin was given, the vaginal secretions generally became definitely acid (pH 5.9 to 5.0 or lower). Vaginal smears never became negative until the pH was 5.5 or less. Cures occurred only when theelin produced an acid (i.e. acid) vaginal pH. Theelin greatly increases vaginal cells which contain glycogen. As these cells break down, lactic acid is produced from the glycogen, forming an acid secretion which destroys gonococci as they cannot live at a pH

greater than 6. Why not therefore acidify the vaginal mucosa in a simple, less expensive way than by endocrines? Karnacky treated about 200 patients with juvenile gonorrheal vulvovaginitis, using acidulated sugar tablets. Results were as good as those from ovarian hormone. Using a somewhat similar glucose tablet, Little also reported good results. Karnacky also obtained good results by "a new hormone method": 40 to 100 c.c. of citrated blood, very rich in hormones, obtained from pregnant women, were injected intragluteally every day for 4 to 5 days or until the children's vaginal secretions changed from alkalinity to an acidity of pH 5.5 or less to nitrazine paper. Marked vaginal metaplasia and acidity of vaginal secretions resulted and smears became promptly negative for gonococci and remained so.

An interesting report on the history of gonorrhea was made by Brodny.

### TUBERCULOUS ARTHRITIS

The general features of tuberculous arthritis were reviewed (Kleinberg; Seddon). It is still common and affected 22 per cent of the 4626 orthopedic patients in the Hospital for Joint Diseases, New York, during 1934 and 1935. Seddon described four clinical stages: 1. In the stage of invasion, physical but not radiographic evidence of arthritis is present. It usually lasts for a few weeks or months. [Occasionally 1 to 3 years.—Ed.] 2. The first stage passes into the stage of tissue destruction, lasting several months, in which radiograms reveal involvement of soft tissue, cavitation and absorption of cartilage. Destruction is due partly to the disease, partly to mechanical factors. 3. In the stage of quiescence the joint is no longer swollen, and serial radiograms show no further destruction of bone but healing has not occurred and the focus still contains many bacilli. 4. In the stage of healing the joint is painless and not swollen. Bone trabeculae reveal more calcium; joint surfaces are more clearly defined. Tuberculous granulation tissue is converted into fibrous tissue in which tubercle bacilli may persist for years. Fibrous ankylosis develops, on the strength of which depends the safety of the joint.

The features of tuberculosis of hip, spine, knee, ankle, shoulder, elbow and wrist were reviewed.<sup>380, 607</sup>

*Tuberculous Spondylitis.* This is the commonest form of tuberculous arthritis. When cervical or lumbar vertebrae are affected symptoms generally precede objective or roentgenographic evidence of disease; the reverse is true when thoracic vertebrae are affected (Kleinberg). Over a period of 17 years Cave studied 122 cases in children. Pulmonary tuberculosis affected 60 per cent. The disease may first affect the intervertebral disk (especially in the lower thoracic or lumbar region), the center of the vertebral body or (most often) its anterior border. Lesions were cervical in 5 cases (4 per cent), thoracic in 94 (77 per cent), lumbar in 19 (16 per cent) and lumbosacral in 4 (3 per cent). Commonest complications were abscess, which afflicted 75 per cent, and paraplegia which afflicted 6.5 per cent (9 patients); of the latter, 4 patients died. Tuberculous joints rarely become fused spontaneously unless there is marked secondary infection. However, in six cases spontaneous intervertebral fusion occurred. Twenty-five pa-



tients had tuberculous arthritis elsewhere. Of the 122 patients 19 (16 per cent) died, eight of them with amyloidosis.

Severe trauma is a rare; mild or moderate trauma is a not uncommon, predisposing factor in Pott's disease (Skolnick). Adams and Decker described some unusual sites of primary tuberculosis in the spine: lateral articulations, spinous processes, and between the head of a rib and the vertebral body.

*Diagnosis of Tuberculous Arthritis.* The following are helpful in diagnosis: a family history of tuberculosis, evidence of preëxisting or coincidental nonarticular tuberculosis, a history of trauma or recent acute infection which may have acted as a precipitating factor, the location of the lesion (temporomandibular involvement is rarely tuberculous; monarticular affections of spine, hip, or knees are likely to be tuberculous) (Kleinberg).

*Roentgenograms.* Clear roentgenographic evidence of tuberculous arthritis may be long absent. At necropsy vertebral bodies are often found completely involved, without previous roentgenographic signs thereof (Adams and Decker). Ferguson likewise concluded that there is no formula for the roentgenographic diagnosis of tuberculous arthritis: "The [roentgenographic] differentiation of tuberculosis from other infections is a matter of perceiving the characteristic expression of chronic and progressive development of effusion, soft tissue atrophy, decalcification, and thinning of cartilage space without productive calcifying reaction." The roentgenologist must have a knowledge of the history and clinical features to help him interpret roentgenograms properly in this disease.

*Blood chemistry.* As would be expected with a purely destructive bone lesion, Mitchell and Crawford found no elevation of serum phosphatase activity in juvenile or adult tuberculous arthritis. There was no correlation between the activity or stage of disease and the phosphatase level.

*Treatment.* Principles of treatment were reviewed (Kleinberg, Cave, Seddon). The value of rest, heliotherapy, dietotherapy and conservative nonsurgical treatment, especially for children, was emphasized. Prolonged rest is required for patients in bed when weight bearing joints are involved. For wrists or elbows simple fixation may suffice; for other joints traction is usually required. Traction or hyperextension should be discontinued when bone destruction stops. To favor ankylosis joint surfaces must not be separated too long; they should be allowed to fall together after three consecutive radiograms taken four months apart show cessation of bone destruction with recalcification and articular "clearing" (disappearance of fluffy outline). When the joint begins to heal and ankylosis begins, supports are needed to protect the "young ankylosis." Fixation operations may then be valuable.<sup>607</sup> [Many still believe that much time and some lives can be saved by early fusion.—Ed.]

Optimal local treatment varies for different joints and ages. Cave and Kleinberg favored prolonged conservative treatment (long immobilization on a convex hyperextension frame) in cases of juvenile Pott's disease.

Fusion was done in 29 of Cave's 122 cases after an average of three years of preliminary conservative treatment; results were satisfactory. No operations, he said, should be done during the acute stage of the disease or during hot summer months. [Some believe that, when necessary, operation at those times is permissible under local anesthesia.—Ed.] Haas, however, favored spinal fusion in children, done as soon as possible, generally within a month of the patient's admission to the hospital. Good results were so obtained in treatment of 80 per cent of 60 patients. In adults Kleinberg favored early spinal fusion but Seddon recommended prolonged conservative treatment prior to fusion. For affected hips prolonged immobilization, then fusion, were favored.<sup>380, 607</sup> For affected knees, shoulders, elbows and wrists of children conservative treatment by immobilization was advised; for adults, early arthrodesis usually seemed preferable although occasionally good results were obtained in elbows by excision and pseudarthrosis.

Fusion was performed by Tregubov in treatment of 147 of 609 patients with tuberculous knees, never in children under eight, rarely in those under 15 years of age, then only after prolonged conservative treatment. Amputation was necessary in five cases; two patients died; other results were quite satisfactory.

#### PNEUMOCOCCAL ARTHRITIS

Pneumococcal arthritis is rare. During 25 years at The Hospital of the Rockefeller Institute only two cases (1 of type I, 1 of type III pneumococcus) were noted in about 1800 cases of pneumonia (Chickering). When present it usually accompanies pneumonia, occasionally pneumococcal septicemia without pneumonia. Usually a monoarthritis, a knee is likely to be affected; less often a shoulder, wrist or elbow. When joints are aspirated for diagnosis smears and cultures should be made. Early cultures may be negative; repeated aspirations may be needed for diagnosis. Most patients are critically ill, often with other complications, and often do not survive. When they do, complete articular function usually is restored. However, cartilage and synovial destruction may result unless joints are aspirated and drained surgically.

A new treatment may now be available, as sulfanilamide seems effective against certain types of pneumococci, especially type III (*mucosus*), according to the following reports.

This was first noted in animal experiments by Domagk (1935, 1936) and by Buttle, Gray and Stephenson (1936). Recent studies on the effect of sulfanilamide on experimental pneumococcal infections were those of Rosenthal, Rosenthal, Bauer and Branham, Gross and Cooper, Cooper, Gross and Mellon and Long and Bliss. Inhibition of pneumococci type I in vitro was noted by Buttle, Parish, McLeod and Stephenson. A few patients with type III lobar pneumonia were favorably affected by sulfanilamide (Heintzelman, Hadley and Mellon). Favorable results were also noted by Long<sup>419</sup> in pneumococcal otitis media but not in pneumococcal meningitis, by Mellon and Bambas in a case of brain abscess from pneumococcus type V, and by Hageman in five cases of pneumonia (type unstated) in three of which empyema

occurred. McIntosh, Wilcox and Wright noted a "favorable effect" in one case of type III pneumococcic otitis media, but questionable results in a similar case and in one case of pneumonia (type III) with empyema. [The doses may have been too small; only 0.9 to 1.2 gm. daily.—Ed.] Mitchell and Trachsler noted a favorable effect in a case of type V pneumococcic meningitis in which sulfanilamide (small doses) and optochin were given, but relief was ascribed to the latter drug. Basman and Perley noted favorable effects in a case of type V pneumococcic meningitis, one of type II pneumococcic septicemia, and one of pneumonia (untyped), but no effect in two cases of pneumococcic meningitis and in one of pneumococcic brain abscess (all type III). Whitby found sulfanilamide, proseptasine and soluseptasine ineffective against experimental pneumococcus type I infections, but two new compounds were definitely protective.

[These must be regarded as preliminary studies. In some cases inadequate doses were given, or ineffective blood concentrations attained; in none was pneumococcal arthritis present. Of particular interest is the recent introduction (1938) of alpha-amino-pyridine-sulfanilamide (M and B 693; daganan\*) which is thought to be more effective against pneumococci than is sulfanilamide.]

### SYPHILIS OF JOINTS

*Charcot Joints.* The features of tabetic Charcot joints described in recent literature were reviewed by Soule. In tabes articular lesions are usually single, and more common in the lower extremities because tabetic cord lesions are generally lumbar. (In syringomyelia joints of upper extremities are more commonly affected due to the high location of the lesion—lower cervical and upper thoracic.) In Soule's case, that of a man aged 47 years with a history of syphilis for 23 years, signs of tabes for 21 years and of tabetic joints for 15 years, unusual features were the multiplicity of lesions (left ankle, right hip, left shoulder), the involvement of areas whose nerve supply is derived from widely separated cord segments, the marked destructive and proliferative articular changes and the marked calcium deposit along fascial planes of foot and leg. Among Lees' 200 cases of tabes were 7 (3.7 per cent) of Charcot joints; in most of the latter signs of tabes were marked but symptoms were few. Tabetic pains or crises were rarely noted in the presence of arthropathy.

*Treatment.* Antisyphilitic treatment alone will not affect Charcot joints but Lees concluded that considerable recovery from tabetic arthropathy may follow treatment if both chemotherapy and orthopedic measures are used. If affected joints are immobilized early and protected from trauma for some months, effusions may subside, ligaments may become taut, new bone and loose bodies may largely disappear and almost normal articular function may return. [Few reports are as optimistic as this.—Ed.] In later cases the best to be expected is ankylosis in a good position. In advanced cases the surgeon can only attempt to provide support by braces or, if this is impossible, to excise the joint. Sometimes massive bone grafts plus chemotherapy give very good results. Few of Lees' patients required surgical treatment and when used it was not very successful. General treatment

\* American name: Sulfanilamide-pyridine (Jr. Am. Med. Assoc., 1938, cxi, 2122).

consisted of tryparsamide intravenously, bismuth intramuscularly; 75 per cent were thus relieved of symptoms.

The fever therapy of early syphilis or early tabes may be an important measure in preventing Charcot joints. *Treponema pallidum* is destroyed in vivo by 5 hours at 39° C. (102.2° F.), 3 hours at 40° C. (104° F.), 2 hours at 41° C. (105.8° F.) or 1 hour at 41.5° C. (106.3° F.) (Boak, Carpenter, Warren 1932). They are made avirulent and immotile in vivo by 1 hour at 42° C. (107.5° F.) or 2 hours at 40° C. (104° F.) (Bessemans and Thiry 1933).

Lees used fever therapy (malaria) in only a few cases resistant to chemotherapy. Marked relief from tabetic pains was usually obtained. Marked clinical and serologic improvement was noted by Epstein in 55 cases of neurosyphilis in which fever and chemotherapy were used. Of five children with congenital syphilis given fever therapy by Speker and McBryde one was cured, two improved; two given inadequate fever were unimproved. "Distinctly encouraging results" were noted in eight neurosyphilitic patients given fever therapy by Williams. Solomon and Kopp concluded that malaria is not as effective in tabes as in paresis; even after serologic tests become negative, tabetic pains or gastric crises may persist and later Charcot joints may appear. Although they approved of fever therapy they regarded chemotherapy for tabes more highly. Simpson and Kendall summarized their results from fever plus chemotherapy for various types of syphilis: of 15 patients with tabes, eight (53 per cent) were markedly improved, six (40 per cent) moderately improved, one (7 per cent) unimproved.

#### BRUCELLOSIS: UNDULANT (MALTA) FEVER

It should be constantly remembered that muscle and joint pains and frank arthritis may be dominant features of brucellosis. Writers are preferring the term "brucellosis" to "undulant fever" or "Malta fever." Although an undulating fever is often the chief feature, the term "undulant fever" is not consistently descriptive, for there is no type of fever pathognomonic of the disease<sup>199</sup>; fever is absent at times, and the term stresses the acute febrile cases to the possible exclusion of the commoner chronic and almost afebrile cases.<sup>295</sup> "Brucellosis" emphasizes the etiology, the *Brucella* organisms.<sup>27, 413</sup> "Bang's disease" is the animal form of the disease.

*Incidence.* Although recognized cases are increasing rapidly, chronic brucellosis is still commonly unrecognized (Evans). Gershenfeld and Butts summarized the incidence and mortality rate in various European countries and in the various American States, with data for each year 1928 to 1934, on the relation of human brucellosis to the local prevalence of Bang's disease in each state. Between 1928 and 1934, 9317 cases (8.7 per 100,000 population) with 374 deaths were reported in the United States; the greatest incidence was in Iowa, Kansas, Vermont and Arizona with 37, 28, 26 and 24 cases per 100,000 population respectively. Of 833,185 herds of cattle tested 38 per cent had infected animals; of about 12,000,000 cattle tested, 8 per cent were "reactors" and were found most commonly in Iowa, Kansas, South Dakota and Illinois. The disease is increasing in many states, an increase only partly due to better recognition.

*Clinical Data.* Thirty papers currently describe the disease as it appeared in almost 700 new cases seen in England,<sup>10, 800, 407, 408, 748</sup> Saskatchewan,<sup>27</sup> South Africa,<sup>90</sup> Arizona,<sup>385</sup> California,<sup>7, 607</sup> Iowa,<sup>741</sup> Kansas,<sup>221</sup> Kentucky,<sup>41</sup> Maryland,<sup>695</sup> Massachusetts,<sup>103, 708</sup> Michigan,<sup>205</sup> Minnesota,<sup>634, 687</sup> New York,<sup>295</sup> North Carolina,<sup>221</sup> Ohio,<sup>450, 740</sup> Oklahoma,<sup>50, 618</sup> Pennsylvania,<sup>220, 387</sup> and Texas.<sup>221</sup>

There are three varieties of *Brucella melitensis*: (1) The melitensis (caprine) strains are limited largely to the goat raising areas of the Southwest; (2) the abortus porcine (or suis) strain, to the hog raising Middle West; (3) the abortus bovine strain is disseminated among cattle widely in the United States (Hardy). All may affect man. The abortus bovine variety rarely affects animals other than cattle and produces mildest infections. Porcine and caprine strains, which also affect cattle, produce more severe disease. In central Pennsylvania, *Brucella abortus* is commoner than *Brucella melitensis*.<sup>337</sup> Evans<sup>222</sup> found the melitensis strains predominant in Charlotte, N. C. and in San Antonio, Tex., less common in Kansas City, Kans. In England *Brucella abortus* prevails (Menton).

Comparing symptoms in 271 cases in California, where bovine strains predominate, to those of Hardy's (1929) 100 cases in Iowa, where porcine strains predominate, Swartout noted certain differences: fever, weakness, sweating, chilliness and headache were commonest symptoms in California; weakness, loss of weight, sweating and anorexia were commonest in Iowa. Joint pains affected 37 per cent of the California, 19 per cent of the Iowa, cases. Symptoms and clinical types of the disease were again reviewed.<sup>103, 100, 221, 413, 741</sup> As noted in previous Reviews the symptoms are protean and the erroneous diagnoses previously made in the cases of Beatty and Harris composed a "staggering list." Characteristic of the disease is the multiplicity of symptoms and the scarcity of physical findings; hence the often repeated dictum, "Think of brucellosis in all cases of prolonged ill defined sickness, in all cases of unexplained fever (especially without localizing signs), in all cases of prolonged disability of the neurasthenic type."<sup>41, 103, 220, 205, 667</sup> Currently stressed were the frequent pulmonary symptoms of brucellosis, often simulating those of tuberculosis.<sup>400, 413, 708</sup> Encephalitis may be produced.<sup>450</sup>

*Symptoms Referable to Muscles and Joints.* Bovine strains rarely produce articular lesions in man, or in animals inoculated experimentally, but melitensis and porcine strains commonly produce them in animals; in man, porcine strains produce arthritis rather commonly but less often than the melitensis (Hardy). In California arthralgia affected 37 per cent of Swartout's patients; in Iowa it was a prominent complaint of 7 per cent, a minor complaint of 36 per cent, of Hardy's patients. Migratory polyarthralgia most often affected knees, elbows, ankles, shoulders, wrists, fingers and toes, and is commonly misdiagnosed "rheumatic fever" (Swartout). Occasionally joints were red, swollen and painful. One case of massive, relatively painless hydrarthrosis was noted (Hardy). Articular residues rarely occur but suppurative arthritis may affect spines and wrists and re-

semble tuberculosis. Cultures of suppurative lesions are likely to be negative *unless the peculiar cultural requirements for Brucella are anticipated.*

Joints are affected in 25<sup>40</sup> to 40<sup>19</sup> per cent of cases. Arthralgia was common among Woodward's 79 cases; it was present in one of seven acute, and in eight of fifty chronic, cases encountered by Baltzan, and in one of Wainwright's cases. Arthritis was less common, affecting only two of Woodward's 79 patients, one of Wainwright's and one of Casey's patients. According to Dustin, the outstanding symptoms in a third of the cases of chronic, afebrile brucellosis are weakness, and muscle and joint pains. Neuritis and neuralgia are common; severe sciatica has been noted (Avery; Evans<sup>222</sup>). Of special interest was the case of Trueman and Allen:

A 52 year old farmer removed the placenta of a cow aborting from Bang's disease; the next day dermatitis (erythema brucellum) appeared; two days later the left knee was stiff and swollen but not red or hot. Roentgenograms showed no osseous changes. There was no fever, leukocytosis or constitutional reaction. Agglutinins were present (1:640) for *Brucella abortus* but smears and cultures of the knee fluid, by several methods, were negative. Three months later the knee was still swollen and a hip was painful.

*Diagnosis.* Confirmation of the diagnosis rests on laboratory procedures, none of which are easy to do or consistently helpful. Their technic, relative value and interpretation were reviewed by several.<sup>27, 50, 103, 220, 223, 265, 266, 332, 467, 468</sup>

Agglutination tests. Some considered these most reliable.<sup>27, 667</sup> "It is vexing to find no accepted standard for a positive test." There is no "diagnostic titer" but strongly positive titers are more significant.<sup>50</sup> Many regard titers of 1:80 or more significant and "positive"; those below 1:80 of little significance. Others, noting proved cases with low titers or negative tests, believe that agglutination tests in any titer should arouse serious suspicions but must of course always be correlated with symptoms and signs.<sup>27, 41, 220, 295</sup> Tests were positive in some dilution in 52 of Beatty's 130 cases; Woodward found agglutinins in 77 of 79 cases (1:80 to 1:2560). Titers gave no index to severity of disease. In all of Swartout's 271 cases agglutinins were present in some (unstated) dilution. [Perhaps this was one of his criteria for diagnosis.—Ed.] Testing 661 patients with fever of unknown origin, the usual causes having been excluded, Campbell and Greenfield found 15 per cent had significant brucellosis agglutinins (1:100 or more in 10 per cent; 1:400 or more in 5 per cent). Gould, Huddleston and their colleagues<sup>850, 851, 858</sup> found agglutinins in only a small percentage of infected patients. During a Detroit epidemic they tested 8124 persons: brucellergen skin tests were positive in 845 (10 per cent); of these 623 were "infected," 222 immune. Only 5 per cent of those infected and 40 per cent of those immune gave "significantly positive tests (1:25 or more)." Of 725 patients with negative brucellergen skin tests, only one possessed significant agglutinins. They regarded agglutination tests as much less reliable than skin tests.

Intradermal test. Others also considered skin tests the most reliable, but these too must be correlated with clinical findings because a positive test may merely represent previous sensitization.<sup>41, 220, 295</sup> Reactions are "negative" unless they remain obvious for 7 to 10 days. Skin tests per se may provoke agglutinins; hence, must not be done prior to agglutination tests.

[Controls should always be used when using skin tests on patients; the antigen is very irritating and often produces a large wheal in normal persons.—Ed.]

**Cultures.** Blood cultures were positive in only eight of Woodward's 79 cases; in only five of Gould's 845 cases with positive brucellergin reactions. They are difficult to make and take 10 to 30 days to grow: "patients are often well by the time reports are back" (Woodward). Kato and Lane recovered organisms in one case by a new method.

**Opsonophagocytic test.** This was again described and interpreted.<sup>265, 266, 332</sup> In the hands of the inexperienced it may be as misleading as agglutination tests (Ervin and Hunt). Foshay and Le Blanc considered it valuable in estimating the efficacy of various remedies; they devised a system for interpreting it numerically.

**Therapeutic test.** This was approved by Beatty. Injections of brucellosis vaccine produce reactions in affected patients but not in others.

**Treatment.** Because the disease may undergo remission or end spontaneously treatments are hard to evaluate. "Any treatment is good if given at the right time" (i.e., near the finish of a wave of fever) (Woodward).

**Chemotherapy.** Of 19 patients treated by Woodward with acriflavine, 11 promptly recovered; results were not good, or were doubtful in eight. The patient of Kato and Lane did not respond to prontosil but did to acriflavine. Mercurochrome was of doubtful value.<sup>741</sup> Wainwright noted a rapid favorable effect from neoarsphenamine in six of seven cases, but Kober considered it of no value in one case. The Abbotts recommended the use of metaphen in early acute cases. Some believe that sulfanilamide and related compounds may prove most useful. Disseptal compounds favorably affect experimental Bang's disease (Hoerlein), sulfanilamide is bacteriostatic to *Brucella abortus* (Nitti, Bovet and Depierre 1937), and patients with undulant fever have apparently been benefited by sulfanilamide (Grouès 1936, Thevenet 1936). Prontosil was ineffective in Kato and Lane's case, and in one of Kober's cases. In the first case the dosage was not stated; in the second it was 2 c.c. b.i.d. for two days. Young's patient presumably responded promptly to injections of foudadin, an antimony preparation.

**Vaccine.** Of 132 patients given *Brucella abortus* vaccine by Harris, 42 per cent were "cured," 36 per cent markedly improved, the rest improved slightly or not at all. Only one of Shuller's four patients responded to vaccine and Beatty considered it only "moderately" successful. The only one of Baltzan's patients relieved by vaccine was one to whom by mistake it was given intravenously instead of subcutaneously; marked fever, shock and rapid improvement resulted. Brucellin, a filtrate of *Brucella*, was regarded by Gould as the most effective method (no results given). Foshay's antiserum was ineffective in one of Woodward's cases and in that of Casey.

**Typhoid vaccine.** Intravenous injections of TAB vaccine gave prompt results in two of Kober's cases, in one case of Shuller and in a chronic case of eight years' duration in which Page gave only one injection (100,000,000

organisms). Harris noted no results in two patients so treated. For certain reasons Snell and Magath could not give specific antiserums or fever therapy to a woman 66 years old with acute brucellosis. She was promptly cured by two injections (15,000,000 and 20,000,000 bacteria) with febrile reactions. Dehydration and disturbed electrolyte metabolism accompanied the reactions but were corrected by the use of physiologic solutions of sodium chloride intravenously, suprarenal cortical hormone and salt by mouth. The course of acute and subacute brucellosis was apparently shortened in 10 cases by intravenous injections of mixed typhoid vaccine given by Ervin and Hunt.

Fever therapy. Three sessions of artificial fever (electromagnetic induction) were given by Zeiter to a patient with recurring fever and joint pains for 10 years, and with changes in one hand simulating atrophic arthritis. The fever promptly subsided and the patient greatly improved but some symptoms of arthritis persisted. [Was the arthritis independent of the brucellosis?—Ed.]

*Mortality.* One of Woodward's 79 patients died of brucellosis. The mortality in the survey of Gershenfeld and Butts was 374 deaths among 9317 cases reported in the United States, 1928 to 1934.

*Prophylaxis.* Infected milk is the chief but not the sole source of the disease for man. "Mercantile interests are still hammering away at the credulous public to sell it the idea of the superiority of raw over pasteurized milk." The public must be educated to the dangers of raw milk. All milk cows must be tested yearly. The disease can be obliterated but the only hope lies in removing diseased animals from domestic herds.<sup>708, 741</sup>

#### TYPHOIDAL ARTHRITIS

No cases of typhoidal arthritis were reported. Those who might see such cases should know that although cultures of typhoid and paratyphoid A and B bacilli were unaffected by sulfanilamide in concentration of 1:10,000 (Long and Bliss<sup>421</sup>), sulfanilamide apparently had a curative effect on experimental typhoid and paratyphoid B infections in mice (Buttle, Parish, McLeod and Stephenson). Schmidt (1936), using prontosil, noted improvement in three cases of typhoid fever. However, a patient with typhoid fever still under treatment with sulfanilamide (doses unstated) was not being benefited, according to Hageman.

#### MENINGOCOCCIC ARTHRITIS

With its parent disease, meningococcic arthritis, which complicates 4 to 7 per cent of cases of meningococcal infection, has been shown to be amenable to treatment by sulfanilamide. Buttle, Gray and Stephenson (1936), Proom and Rosenthal, Bauer and Branham demonstrated the protective action of prontosil against meningococci in mice. Whitby found sulfanilamide and a new compound effective, but proseptasine and soluseptasine ineffective against experimental meningococcal infections. Sulfanila-



mide was successfully used by Schwentker, Gelman and Long in 10 cases of meningococcic meningitis (two with arthritis) and one with septicemia alone. The effect was good in all cases and comparable to that from specific antiserum. The drug was injected intraspinally (total dose of 10 to 30 c.c.) and subcutaneously (100 c.c. for each 40 lbs. body weight) every 12 hours for two days and once daily thereafter until improvement was noted. Krusen and Elkins reported a case of meningococcemia (rash, pains in arms and legs, positive blood culture but no meningitis) in which relief was not given by specific serum; cultures became temporarily negative (for one week) after three sessions of fever (two of 10 hours each and one of 6 hours at 106.5° F.). Prontosil was then given intravenously; the patient promptly recovered although her nasopharynx contained meningococci a year later. Sulfanilamide promptly cured five patients with meningococcus meningitis (without arthritis) seen by Carey, two seen by Basman and Perley and one each seen by Harvey and Janeway and by Brown and Bannick. Some of them had not responded to serum; the spinal fluid of several became sterile within 24 hours after using sulfanilamide. Of two patients so treated by McIntosh, Wilcox and Wright results were favorable in one, "questionable" in one. Three patients of Mitchell and Trachsler rapidly recovered after combined treatment with prontosil orally, 1 per cent sulfanilamide solution (10 to 20 c.c. intraspinally daily), specific serum and antitoxin. A six weeks' old baby with acute suppurative meningococcal arthritis but no meningitis was rapidly cured by Long and Bliss<sup>425</sup> who gave sulfanilamide subcutaneously once (0.6 gm. in 100 c.c. saline) and in milk thereafter for six days.

The combined use of serum and sulfanilamide for meningococcic infections in animals seemed to Branham and Rosenthal to be superior to the use of either alone. The drug alone was more effective when given subcutaneously than orally; a high percentage of treated animals survived fatal doses of bacteria even after only one injection of the drug.

#### SUPPURATIVE (PURULENT, SEPTIC) ARTHRITIS

New cases reported were caused by the usual bacteria, *Staphylococcus aureus* and *albus* most often, hemolytic or green-producing streptococci, pneumococci, gonococci and rarer bacteria occasionally. Clinical features of the 69 new cases conformed to those described in previous Reviews.<sup>73, 329, 370, 393, 504, 574</sup> Two points were emphasized: symptoms of suppurative arthritis are much more severe than those of ordinary "infectious arthritis"; patients often dread the slightest motion of bed or bed clothes; in acute monarticular suppurative arthritis juxta-articular osteomyelitis must be suspected. Of 80 patients with acute hematogenous osteomyelitis seen by Robertson, 20 developed adjacent suppurative arthritis: a hip was involved in 11; a knee in 6; ankle, sacro-iliac and elbow joint once each. Hosford reported 12 cases of suppurative arthritis of hips; in six there was adjacent osteomyelitis. Brockway noted eight cases without osteomyelitis

(knee in five, hip in two, ankle once) and 12 cases secondary to osteomyelitis. The case of Oldham was unusual: suppurative arthritis (hemolytic streptococci) of an elbow secondary to an old infected varicose ulcer of a leg; it responded promptly to rest, aspiration and prontosil.

It was again emphasized that roentgenograms are of no value in diagnosis during the first 10 days unless they reveal adjacent osteomyelitis; most important for diagnosis is early aspiration and culture of articular exudate.<sup>329, 370, 393, 574</sup>

*Treatment.* Prompt, complete evacuation of infective effusions by repeated aspirations and lavage, or if necessary by incision and drainage, is indicated. Traction may be necessary to prevent spontaneous dislocation. Physical therapy and motion are necessary as soon as possible but not until temperatures are normal at least a week. Brockway favored salt pool baths after drainage; his patients without osteomyelitis recovered complete function in from 3 to 5 months, the others took an average of 16 months to recover. Of Hosford's 12 cases recovery was complete in six, with 20 degrees motion in two and ankylosis in four. In Robertson's 20 cases results were excellent in 12, poor in four; four patients died. Although Domagk (1935) and Mellon, Shinn and McBroom noted therapeutic effects of sulfonamide compounds on experimental staphylococcal infections including staphylococcal arthritis, striking results in such human infections have not been noted. Mitchell and Trachsler's patient with staphylococcal septicemia and pyarthrosis was unrelieved by sulfanilamide.

#### ARTICULAR DISEASES DUE TO HEMOLYTIC STREPTOCOCCI

Certain nonsuppurative or suppurative articular complications may accompany diseases due to hemolytic (or beta) streptococci; e.g., puerperal sepsis, scarlet fever, hemolytic streptococcal osteomyelitis, streptococcic sore throat or otitis media and hemolytic streptococcemia. It is now more important than ever to recognize promptly the bacteriologic identity of these articular complications because of the discovery that sulfanilamide is so effective against certain hemolytic (or beta) streptococci.

*Classification of Streptococci.* Streptococci were divided by Smith and Brown, 1915, and by Brown, 1919 to 1920, into three main varieties: (1) *Streptococcus viridans* (alpha or green-producing streptococci); these produced in blood broth no hemolysis, on blood agar green pigmented areas around their colonies with areas of partial hemolysis; (2) *Streptococcus hemolyticus* (or beta streptococci); these produced in blood broth hemolysis of erythrocytes, on blood agar zones of clear hemolysis around each colony with no intact erythrocytes adjacent to the colonies (beta type of hemolysis or "beta hemolysis"); (3) nonhemolytic (gamma or indifferent) streptococci; these produced no hemolysis or green production either on blood agar or in blood broth. Brown noted another type of streptococcus (alpha prime streptococcus) with characteristics intermediate between alpha (viridans) and beta (hemolytic) streptococci. In blood broth the alpha prime

variety produced no hemolysis, on blood agar it produced slight hemolysis—definite zones of colorless hemolysis, but this type of hemolysis ("alpha prime hemolysis," produced by alpha prime streptococci) could be distinguished from the true type of hemolysis ("beta hemolysis" produced by beta [hemolytic] streptococci) in that microscopic examination showed a more or less dense fringe of nonhemolyzed erythrocytes next to the alpha prime colony. To this extent then not all hemolytic streptococci are beta streptococci (some hemolytic streptococci being of the alpha prime variety). Sulfanilamide is effective against beta (hemolytic) streptococci but not against alpha or alpha prime (hemolytic) streptococci. Therefore to distinguish clearly which streptococcal infections are being effectively treated with sulfanilamide current writers are speaking not of "beta or hemolytic streptococci" but of "beta hemolytic streptococci" and of "beta hemolysis" (in distinction to alpha prime hemolytic streptococci and "alpha hemolysis").

There are many different groups of each of these three main varieties of streptococci and each of these groups in turn is composed of a number of distinct types. Thus there are many different strains (or types) of hemolytic streptococci: those of scarlet fever, those of erysipelas, those of puerperal fever, etc. Furthermore, bacteriologists speak not only of different strains of hemolytic (or other types of) streptococci but also of different strains of scarlet fever hemolytic streptococci; for example, a bacteriologist studies 50 "strains" of scarlet fever streptococci, meaning the individual strains (all hemolytic) isolated from 50 different cases of scarlet fever.

Lancefield (1933), studying 106 strains of hemolytic streptococci, isolated from a wide variety of diseases and patients in various parts of the world, was able to group practically all of them into five main groups (A, B, C, D, E) differentiated serologically by means of the precipitin reaction, but not differentiable by agglutination reactions. Group A was composed largely of strains of human origin. Group B was obtained from normal cows' milk and from cases of bovine mastitis. Group C was obtained from various lower animals; its members produced equine strangles, endometritis, etc. Group D was isolated from cheese. Group E was found in certified milk. Various strains of *Streptococcus viridans* did not fall into any of these groups. The group-specific substance in the strains of hemolytic streptococci groups A and B (and probably the others also) was identified as a carbohydrate. Thus, Lancefield found a close correlation between the groupings and the animal source.

Later this differentiation was modified and extended by Lancefield and Hare (1935), Plummer (1935) and Hare (1935). It was found that the main reservoir of group A strains was the human nasopharynx. Although the chief source of groups B and C hemolytic streptococci was not human, a few strains of groups B and C hemolytic streptococci were found in normal and sick humans. Four new groups were discovered (F, G, H, K). These groups were occasionally found in humans, generally as nasopharyngeal (occasional vaginal) saprophytes, but rarely caused disease and when they did the disease was slight.

[This was the opinion in 1935.—Ed.]

In summary, to date nine serologic groups (A, B, C, D, E, F, G, H, K) of hemolytic streptococci are recognized but the vast majority of the hemolytic streptococci that cause acute and serious diseases in man belong to group A. Thus, all strains of hemolytic streptococci isolated in scarlet fever and practically all strains from puerperal fever and erysipelas belong

to group A (Plummer 1935). The hemolytic streptococci belonging to the other groups are isolated usually from animals; rarely from man. When present in man, they are found acting mostly as saprophytes; they are only rarely the cause of disease of man and then only of mild disease. [Newer work does not uphold the latter contention; some group B strains fatal to man have been noted.—Ed.]

It is fortunate that most of the hemolytic (or beta) streptococci seriously pathogenic to man belong in group A (Lancefield) because sulfanilamide is effective against this group of hemolytic streptococci. We have already reviewed some of the pioneer work on the effect of sulfanilamide on hemolytic and other streptococci (Domagk 1935, 1936; Tréfouël, Tréfouël, Nitti and Bovet 1935, Hörlein 1936, Colebrook and Kenny 1936, Lavaditi and Vaisman 1936, Buttle, Gray and Stephenson 1936, Colebrook, Buttle and O'Meara 1936, Vermelin and Hartemann 1936). Full details of this work are found particularly in the papers of Long, Long and Bliss, and Bliss and Long and in the new book of Mellon, Gross and Cooper (1938). Briefly, sulfanilamide (in concentrations of 1:10,000) and related compounds are markedly effective against group A (hemolytic) streptococci, effective also against groups B and C but ineffective against group D or G<sup>419, 423</sup> (in vitro).

[Recent reports indicate that sulfanilamide is effective in vivo against all beta hemolytic streptococci except groups D and F. Although sulfanilamide inhibits the growth of alpha hemolytic streptococci, gamma streptococci and certain other bacteria in vitro, it is apparently not effective against alpha or gamma streptococcal infections in vivo.—Ed.]

Early foreign reports indicating the beneficial effect of sulfonamide compounds on hemolytic streptococcemia with articular complications were those of Lampert (1935) and Snyers (1936). Foulis and Barr promptly cured a patient with puerperal sepsis and metastatic arthritis as did Scal a patient with hemolytic streptococcemia with metastatic arthritis. With protosil and sulfanilamide Basman and Perley promptly cured a patient with hemolytic streptococcemia, meningitis and arthritis. In a case of hemolytic streptococcemia with pyogenic arthritis and other complications, and in which Mitchell and Trachsler gave sulfanilamide, the patient rapidly recovered but articular destruction had already occurred.

[In such infections one of us, A. J. K., has noted incomplete relief from sulfanilamide; supplementary surgical treatment may be required.—Ed.]

#### ARTHRITIS OF SCARLET FEVER: POSTSCARLATINAL RHEUMATISM

There are three articular complications of scarlet fever: (1) non-suppurative scarlatinal arthritis with sterile exudates, (2) suppurative scarlatinal arthritis with hemolytic streptococci in purulent exudates and (3) scarlatinal or postscarlatinal rheumatism—an acute form of polyarthritis representing latent rheumatic fever activated by scarlatinal streptococci.

The incidence of scarlatinal arthritis (types 1 and 2) was 99 cases (1.8 per cent) among 5549 patients with scarlet fever seen by Boyd between 1933 and 1936. Excluding 1936, when convalescent serum was often used, the incidence was 85 (2 per cent) among 4077 cases, an incidence lower than that previously cited, probably because of the recent mildness of the disease.

*Type 1.* In Boyd's series, nonsuppurative scarlatinal arthritis affected females (70 patients) oftener than males (29 patients); older children and adults oftener than young children. It may occur any time in the course of the disease, but usually between the fourth and tenth days, and generally it affects a few small joints symmetrically, often in rotation. Generally subsiding in two to five days, it may recur briefly a week later. Symptoms are increased fever, stiffness, fairly severe pain, slight tenderness, swelling from effusion and periarticular involvement. Some would classify this type with type 3 as also a manifestation of rheumatic fever (e.g., Paul, Salinger and Zuger, 1934). But Boyd considers it a toxic form of arthritis unrelated to rheumatic fever because not a single case was complicated by endocarditis. Treatment included methyl salicylates externally and salicylates orally; of the latter, 5 grains to young children, 10 grains to older children, 20 grains to adults every 3 to 4 hours. When not tolerated orally, salicylates can be given morning and evening by rectum, half the daily dose in 4 ounces of starch paste.

*Type 2.* Suppurative arthritis was rare in Boyd's series: three cases among 5549 patients. The three patients were seriously ill with hemolytic streptococcemia. Affected were a knee in one case, a knee and wrist in one, a finger in the third. Joints were painful, swollen, red, hot and tender. The patients recovered under treatment by scarlet fever antitoxin, convalescent serum, sulfanilamide, repeated transfusions, and incision and drainage of joints.

*Type 3.* Many patients with inactive rheumatic fever escape exacerbations thereof during scarlet fever but Boyd noted two who did not. Rheumatic fever may be precipitated during or just after scarlet fever; its exact relationship thereto is not fully understood.

Arthralgia affected 3 per cent of young adults being immunized against scarlet fever by Healey. Generally appearing within 12 hours after a dose of scarlatinal streptococcus toxin the arthralgia, with or without swelling, lasted a few hours to several days, disappearing without residue. To determine the cause of these joint pains Healey gave to different groups of 63 patients: (a) unheated toxin in broth media, (b) the toxin heated to destroy the soluble toxin and (c) diluted broth media containing no toxin. Arthralgia was produced only by the toxin in 75 per cent of cases, chiefly but not solely by the toxin in 17 per cent, by proteins of broth and not by the toxin in 8 per cent. Since 84 per cent of these 63 patients had previously had arthralgia or rheumatic symptoms suggestive of streptococcal infection, Healey concluded that patients, so affected previously, are sus-

ceptible to subsequent provocation of arthralgia by unrelated toxins including the scarlatinal.

*Treatment with Sulfanilamide.* Definite conclusions on the value of sulfanilamide in scarlet fever cannot be drawn from the earlier work; details were scanty and dosage often low (Püschel 1935, Scheurer 1936, Maraun 1936). Recent results have been more definite. Peters and Havard treated 150 patients with "proseptasine" and 150 patients otherwise. The average duration of fever was greater in the sulfonamide-treated group than in the control cases but none of the former patients died, against two in the control group. Complications affected only 35 per cent of the drug-treated group, 56 per cent of the controls. In particular, invasive phenomena: e.g., endocarditis, rheumatism, were distinctly less common among those receiving sulfonamide: "Rheumatism" affected only 2 per cent of those treated with sulfonamide; 6.6 per cent of the others. Other writers,<sup>421, 422, 530</sup> without referring to scarlatinal arthritis, noted favorable results. In Hageman's eight cases the toxic phase was unaffected by sulfanilamide but no complications arose. The results of others have been less definite.<sup>38, 459</sup>

### RHEUMATIC FEVER

*Incidence.* Many new statistics were reported on the incidence and clinical manifestations of rheumatic fever and rheumatic carditis in various parts of the United States, England, Australia, New South Wales, China, Malaya (Dicum), and the Punjab. Among 33,297 Philadelphia school children (11 per cent of the total) Cahan found 159 with suspected and 191 with definite carditis; of the latter, in 129 the condition was rheumatic and in 18 "probably rheumatic." Although rheumatic fever is common in London, Cove-Smith stated that "flagrantly acute cases" are becoming increasingly rare; responsible factors were a gradual attenuation in virulence during the last 20 years, higher standards of living, improved nutrition, and the prophylactic work of the London County Council. Rheumatic carditis is much commoner in Bristol, England (1.9 cases per 1000 total population; 7.7 per 1000 school population) than in nearby cities; for example, the rate in Bath was only 0.2 per 1000 total population, 1.3 per 1000 school population (Perry and Roberts). Wallace found the disease definitely increasing in Edinburgh; a hospital incidence of 5.6 per cent of the total medical admissions was noted in 1934. In the state of Victoria, Australia (population 1,852,171) there are yearly about 1303 new cases of rheumatism (rheumatic fever, chorea, or carditis), a rate of 0.7 per cent, and 1 per cent of the population have cardiac rheumatism (Graham). In New South Wales the incidence of rheumatic carditis (0.3 to 0.6 per cent in different hospitals), was much less than that in Europe or the northern United States but much greater than that in the tropics (Maddox). Among 62,991 country school children in New South Wales, 2.7 per cent had "rheumatism" and 0.6 per cent had rheumatic valvulitis. In north

China the incidence of rheumatic fever and chorea is higher (0.57 per cent of all medical admissions) than previously reported but considerably less than that in European and northern American cities (Chang and Dieuaide); it approximated that of St. Louis.

*Predisposing Factors.* 1. Geography and climate. Further evidence was presented to show that the disease is more prevalent in the North than in the South. Paul and Dixon examined American Indian school children on reservations in Montana and Wyoming, northern New Mexico and northern Arizona and in southern Arizona. Definite rheumatic carditis was found in 31 of 688 children (4.5 per cent) in the two northern regions; in 21 of 1106 (1.9 per cent) in the two central regions; in only 5 of 1019 (0.5 per cent) children in the southern group. Thus, the disease was almost 10 times more frequent in the North than the South. Significance was attached to its frequent occurrence in the cold but dry climate of Montana and Wyoming where it was twice as frequent as it is in New England (2.2 per cent incidence). Sharp and John compared the incidence in Chicago and in Galveston, Texas. The incidence of rheumatic carditis without arthritis was 0.35 per cent of hospital admissions in Chicago, 0.08 per cent of those in Galveston. "Acute rheumatic affections" were about six times more frequent in the North. Acute rheumatic fever without chorea or carditis occurred about four times, chorea about 33 times more often in the north. However, old rheumatic carditis occurred almost as often in Galveston as in Chicago. Hence, the southern climate apparently affords its residents much more protection against chorea than against other rheumatic affections, and diminishes the severity more than it does the incidence of rheumatic fever. Seasonal variations in the incidence of throat infections with hemolytic streptococci were noted and somewhat paralleled those of rheumatic attacks but not sufficiently to consider the throat infections the chief factors in the rheumatic attacks. In New South Wales the distribution of "rheumatism" \* was fairly even over the country but rheumatic carditis was more frequent on tablelands and slopes than in coastal regions (Maddox).

Kamra emphasized that rheumatic fever does exist in the Punjab. Of 1000 patients examined, two had "acute articular rheumatism," six had rheumatic endocarditis. In one village the incidence of rheumatic fever was 2.13 per 1000 of the total population, an incidence comparable to that in England.

2. Season. Only 13 per cent of the Galveston cases occurred between June and September; in Chicago the summer reduction was not nearly so striking (Sharp and John). Among the 141 Chinese cases of Chang and Dieuaide, 39 per cent of attacks came in winter (Dec.-Feb.), 35 per cent in spring (Mar.-Apr.); an abrupt rise occurred in December, a rapid fall in June. The seasonal curve differs from that of New York in its wider

\* In this section on rheumatic fever it is to be understood that "rheumatism" and "acute rheumatism" mean "rheumatic fever" or "the rheumatic state."

range from winter to summer, and from that of Glasgow in the absence of any autumnal rise. The distribution in Peiping was somewhat similar to that of San Francisco. In Sydney, Maddox noted no definite seasonal incidence among hospitalized patients.

3. Social and hygienic factors. Contiguity was an important factor in the incidence of rheumatic carditis. In Dewsbury, England, most patients were from the most congested part of town (Elder). In Bristol there was a "large and highly significant association" between the incidence of the disease and the density of school children per room in the various city wards (Perry and Roberts). In Sydney, Australia, most of the patients were from the poorer industrial quarters of the city, very few from the better class suburbs.

4. Family and heredity. The incidence of rheumatic fever or carditis in families of nonrheumatic children was only 5 per cent (Wallace); that in families of rheumatic children was 23 per cent in Cahan's series, 30 per cent in Wallace's series, but only 11 per cent in Maddox's cases and only 8 per cent in those of Chang and Dieuaide. The latter consider such data generally unreliable. The previously reported familial incidence has ranged from 15 to 58 per cent. Three factors have been held responsible; (1) a common environment, (2) communicability, (3) susceptibility, probably on an hereditary basis, resulting from a familial weakness of tissues of mesenchymal origin, a familial lack of natural protection against the disease. Connor accepted the latter explanation. As a result of a thorough study of 112 rheumatic families [which study deserves more attention than we can give it here.—Ed.] Wilson and Schweitzer concluded that an hereditary factor, transmitted as a single autosomal recessive gene, is distributed among the population, which makes the bearer susceptible to rheumatic fever. The exact rôle of environment and contagion could not be determined. Hereditary susceptibility seemed to determine the familial incidence of rheumatic fever but it may not necessarily be the sole condition essential for its development.

Wilson and Schweitzer studied 112 rheumatic families comprising 468 rheumatic children aged three years or more; the families were observed for an average of nine years. Although unfavorable environment increased the incidence it was not responsible for the observed familial incidence. Nor was communicability found to be the chief factor. More important was the hereditary factor. Of the 112 families, in 50 per cent (55 families) one or both parents were rheumatic; in the remaining 57 families neither parent was rheumatic, but in 46 per cent of these 57 families there were rheumatic persons on the maternal or paternal side. Thus, in only 28 per cent of the entire 112 families was there no family history of rheumatism. Of four sets of identical twins all were alike in having rheumatic fever; of 12 pairs of fraternal twins, five had similar experiences (i.e., both were either affected or were free) and seven were dissimilar in experience. The hereditary mechanism involved a single autosomal recessive gene. Dominance involving one or more genes, recessives involving two or more genes, and sex linkage were all excluded.

[Such a study on the heredity of atrophic and of hypertrophic arthritis would be very valuable.—Ed.]



5. Sex. Among 750 juvenile patients with rheumatic fever studied in New York by Roth, Lingg and Whittemore, 54 per cent were females; among 488 patients with rheumatic carditis 51 per cent were females. In Australia, of 382 rheumatic rural children 51 per cent were females, of 428 urban children, 47 per cent were girls.<sup>435</sup> Of 141 Chinese patients (including adults) with rheumatic fever, 38 per cent were females.<sup>107</sup>

6. Age. The patients of Chang and Dieuaide included adults. The disease appeared before the age of 30 years in 82 per cent, most often at the age of 14 years. In Australia children hospitalized for rheumatic fever were most frequently nine years old at the onset of their disease. Among the 488 cases of juvenile rheumatic carditis reported by Roth, Lingg and Whittemore the mean age at onset was eight years; the mode seven years. A fourth of initial affections occurred in preschool ages. The mode age of onset varied with the manner in which the disease first appeared: in polyarthritis it appeared about the age of five; in carditis, about six; in chorea, between seven and eight years of age. Leonard confirmed the observation of others that the factor of age is important and that if a child escapes acute rheumatism prior to puberty (age 13 to 15) he is likely to escape it entirely or be affected much less severely. Leonard studied 500 children with rheumatic fever; 71 per cent developed carditis. The initial attack generally came between the ages of 5 and 11 years. He observed 100 patients for several years; all had at least one recurrence; 60 per cent had two. At or about puberty there was a sharp decline in the incidence of both initial attacks and recurrences.

*General Symptomatology.* "Nervousness" has been considered characteristic of rheumatic or "prerheumatic" children. Neustatter could not confirm this impression: rheumatic children are more nervous than normals but no more so than those with other illnesses; rheumatism may aggravate a child's tendency to nervousness but does not cause it. The "typical rheumatic child" was again described.<sup>13</sup> Among the 488 cases of juvenile carditis seen by Roth, Lingg and Whittemore initial symptoms were: polyarthritis alone in 45 per cent, with carditis in 16 per cent, with chorea in 4 per cent, with chorea and carditis in 1 per cent (i.e., polyarthritis in a total of 66 per cent); carditis alone in 14 per cent, with chorea in 1 per cent; chorea alone in 19 per cent. Polyarthritis was the most common initial sign among both girls and boys; as an initial manifestation chorea, with or without carditis, affected girls more often than boys.

Among Maddox's 428 cases of juvenile acute rheumatic fever, early symptoms were arthralgia in 97 per cent, arthritis in 28 per cent, sore throat in 23 per cent, vomiting in 9 per cent, abdominal pain in 8 per cent, cough or cold in 8 per cent, stiff neck in 3 per cent, choreiform motions in 1.5 per cent; rashes, generally morbilliform, in 14 per cent, pyelitis in 2 per cent, nodules (rare in Sydney) in only 1.5 per cent. [This low incidence of nodules is not satisfactorily explained.—Ed.] Carditis affected 59 per cent of the total: 46 per cent of 308 in their first attack, 64 per cent of 120 in their second attack. In those so affected endocarditis appeared with great rapidity. Pericarditis was present in 2 per cent of 396 nonfatal cases, in 13 per cent

of 32 fatal cases. . Only 16 per cent of the 428 patients had valvulitis without previous febrile rheumatism or chorea. In Sydney therefore the clinical features differ little from those noted elsewhere except for the absence of a seasonal incidence and the rarity of nodules.

The clinical features in the 141 Peiping cases, adults and children (Chang and Dieuaide) were carefully analyzed: present were fever in 97 per cent, polyarthritides in 92 per cent, leukocytosis in 83 per cent, carditis in 64 per cent, anemia in 60 per cent, headache in 28 per cent, congestive failure in 22 per cent, nausea in 20 per cent, precordial pain in 19 per cent, skin lesions in 17 per cent, vomiting in 16 per cent, nodules in 15 per cent, pleurisy in 13 per cent, epistaxis in 13 per cent, pericarditis in 12 per cent, hematuria in 11 per cent, abdominal pain in 11 per cent, chorea in 9 per cent and bronchopneumonia in 4 per cent. Also reported were the incidence of polyarthritides, carditis and chorea alone and in combination, the various joints affected, types and combination of cardiac lesions, site of nodules, etc.

Among 73 rheumatic patients seen by Massell and Jones the following appeared: fever in 53 per cent, nodules in 41 per cent, chorea in 29 per cent, epistaxis in 25 per cent, joint pains in 23 per cent, rash in 19 per cent, precordial pain in 19 per cent, congestive failure in 18 per cent, abdominal pain in 14 per cent, pneumonia in 10 per cent, pericarditis in 7 per cent and pleurisy in 4 per cent.

The first symptom of rheumatic fever among Wallace's 516 juvenile cases in Edinburgh was chorea in 44 per cent, arthritis in 37 per cent, "primary carditis" in 19 per cent. During the first attack carditis developed in 53 per cent.

*Special Clinicopathologic Data.* 1. Heart. The clinical and statistical data on rheumatic carditis in current literature are too voluminous to be summarized here. For details reference must be made to the original reports.<sup>13, 93, 107, 306, 387, 435, 587</sup> They emphasize again the tragic and enormous morbidity and mortality from rheumatic carditis. Rheumatic carditis should be regarded as the chief manifestation, not a complication, of rheumatic fever.<sup>306</sup> In 1930, when the population of the United States was about 122,000,000, there were about 840,000 cases of rheumatic carditis in the country (Paul 1930); now with a population of about 130,000,000, it has been estimated that there are over 1,000,000 Americans with rheumatic carditis (Hedley). In Canada there are 25,000 school children with rheumatic carditis, 3000 in Montreal alone (Cushing). A child 10 years old is three times as likely to die from carditis as from any other disease. Rheumatic fever is responsible for from 15 to 40 per cent of carditis at all ages, and for 90 per cent of all juvenile carditis in the United States. Rheumatic carditis annually causes 40,000 deaths in the United States, the average age at death being 30 years (Hedley). In Dewsbury, England, 70 per cent of juvenile carditis was rheumatic (Elder). Observing 337 patients with rheumatic fever over a period of 20 years Wilson found the heart practically always (eventually) affected. Even in early attacks only about one patient in every four escapes carditis, but patients with chorea seem to develop carditis less frequently (Warner). Warner emphasized an "extraordinary fact": If a child survives two attacks of chorea without developing carditis he never seems to develop carditis in future attacks of chorea. In cases of juvenile rheumatism, carditis and polyarthritides were so frequently associated, and patients thus affected thereafter

ran so true to type as to suggest to Roth, Lingg and Whittemore that they represent a similar method of response. Many patients (25 to 50 per cent) with juvenile rheumatic carditis give no history of fever, acute polyarthrititis or chorea; this was so in 50 per cent of 43 cases of rheumatic carditis seen by Sherwood at necropsy.

A basal pericarditis appeared to Wolffe and Digilio to be the earliest manifestation of low grade juvenile rheumatism; it produced in the left second and third costosternal junctions, occasionally at the apex, a somewhat musical friction-like murmur, generally systolic, occasionally diastolic, sometimes transitory and often misinterpreted as due to mitral or aortic valvulitis or pulmonary arteritis.

The significance of cardiac murmurs has been overstressed, that of heart tones understressed: from the intensity of the first heart sound Keith believed he was able to predict the length of P-R intervals with fair accuracy. An accentuated first sound is more diagnostic of mitral stenosis than the middiastolic murmur. Heart valves are relatively immune to damage from rheumatic fever in adult life for reasons not yet clear. Kugel and Gross (1921, 1926) confirmed Langer's finding (1880) that fetal valves possess blood vessels but most adult valves do not; it was concluded that when valvular vessels do not regress but remain patent in adults they render the patient liable to embolic valvulitis. This explanation is unsatisfactory to some. Gross now believes that only very rarely do normal valves possess blood vessels; vascularity even in normal-appearing valves is almost always the result, not the cause, of antecedent rheumatic inflammation. According to Wearn and Moritz, however, 84 per cent of normal heart valves possess blood vessels; active or healed valvulitis can be found in the absence of blood vessels, and the incidence of blood vessels in a given valve does not correspond to the incidence of rheumatic valvulitis in that valve. Conner concluded that differences in the reactions of juvenile and adult valves to rheumatic fever depend not on the vascularity of a valve but on differences in the disease itself in the two age groups.

Uncomplicated aortic insufficiency is extremely benign (Conner). Patients so afflicted are able to pursue lives normal in activity and length and die ultimately of some other disease unless they develop (as they sometimes do) subacute bacterial endocarditis. Patients with aortic stenosis, once failure supervenes, die quickly; this was again noted by Thompson and Levine who, however, noted the paradox that although patients with tricuspid stenosis may die early, they are able to tolerate their symptoms considerably longer than those whose tricuspid valves are not affected. Auricular thrombi may result from severe mitral stenosis, congestive heart failure and auricular fibrillation. Appropriate stains will distinguish the fibrin material in thrombi from the focal swelling of collagen (fibrinoid swelling of Klinge) in the same tissue (Graef, Berger, Bunim and Chappelle). Rae noted a case of presumed leukemia (leukocytes 76,000) proved at necropsy to be one of acute rheumatic fever with coronary aneurysms

and thrombosis with infarction, the leukocytosis being a response to the thrombosis. Other reports of interest were on the effect of rheumatic carditis on the superior vena cava (Waalder), on the development of experimental endocarditis with an extensive review of literature (Nedzel), and a critical historical appreciation by Keil of the work of Wells (1812) who first described rheumatic nodules and was one of the first to emphasize the relationship of carditis to rheumatic fever.

2. Joints. Fisher examined synovial membrane from a sternoclavicular joint of a young girl dead after four weeks of rheumatic fever. Present were many of the specific pathologic reactions seen in rheumatic hearts: areas of fibrinoid degeneration in synovial villi and membrane and in the subintima of blood vessels; vascular endothelial proliferation and perivascular cellular reactions resembling Aschoff bodies. According to Fisher, areas of fibrinoid degeneration (first described by Neumann 1880, 1896, recently by Klinge, 1932) are not specific for rheumatic fever but are also seen in synovial membranes in atrophic arthritis.

3. Muscles. It is important to distinguish fatigue pains or nonrheumatic "growing pains" of children from "true rheumatic growing pains"; the latter occurred early in many of Wallace's rheumatic children. All children have muscle pains on occasion (present in 13 per cent of 600 nonrheumatic children) but Wallace regarded as significant pains severe enough to keep children from school two to three days. Normal growth does not cause pain. Muscle pains due to fatigue or poor posture generally affect lower extremities and appear after exercise or at the end of the day. Rheumatic pains generally affect upper extremities also, are not especially related to exercise and appear any time of day although especially at night (Rothbart).

4. Nodules. These were present in 15 per cent of the 141 cases of Chang and Dieuaide. The histopathology of subcutaneous nodules in rheumatic fever was carefully described by Mote, Massell and Jones, and by Collins. It was compared to that of induced nodules in rheumatic fever, spontaneous nodules in atrophic arthritis and those from trauma in non-rheumatic patients.

The sequence of events in the evolution and regression of rheumatic nodules was (Mote, Massell, Jones): a structural alteration in collagen, resulting edema and deposition of fibrin-like material; concurrently or shortly thereafter vascular damage and polymorphonuclear leukocytic and lymphocytic infiltration, with proliferation of primitive perivascular mesenchymal and other cells which invade the borders of the altered collagen foci; subsequent gradual organization progressing from perivascular areas toward the centers of the necrotic foci; concurrently a typical cell reaction—closely packed, radially arranged, basophilic mononuclear and multinuclear cells which stain somewhat like fibroblasts and which can deposit intercellular collagen. The outcome is a progressive organization to normal replacement of the lesion with fibrous tissue.

Subcutaneous nodules were induced by Massell, Mote and Jones by injecting 2 to 3 c.c. of the rheumatic patient's own blood into the olecranon

region; in some cases, friction was applied daily thereto. Regardless of this, 45 per cent of 82 rheumatic patients developed induced subcutaneous nodules essentially similar to the spontaneous type. Only one of 34 non-rheumatic persons so treated developed nodules.

[Similar experiments should be made on patients with atrophic arthritis, hypertrophic arthritis and even gouty arthritis.—Ed.]

A discussion of the comparative pathology of the nodules of rheumatic fever and of atrophic arthritis will be given later.

5. Lungs and pleura. Gouley again described "rheumatic pneumonia" and pneumonitis, the latter being a lesser degree of lung involvement without consolidation. Often seen, they are part of rheumatic fever, not complications, but are often overlooked as they are transient. Signs are more striking than symptoms. An occasional complication is basal pulmonary atelectasis or "inflammatory collapse," which may be the basis for Ewart's sign. Due to the interstitial fibrosis that follows rheumatic pneumonitis, lungs may never return to normal. The resultant respiratory insufficiency is probably a factor in the right ventricular failure heretofore blamed entirely on mitral stenosis.

In the Peiping series,<sup>107</sup> pneumonia affected 3.5 per cent, and pleurisy affected 13 per cent of the 141 patients. The incidence of rheumatic pleurisy has been given as from 3 to 10 per cent. It affected only two of Gouley's 25 patients with rheumatic pneumonia who came to necropsy. In Edstrom's group of 850 patients with rheumatic fever pleurisy affected 4.5 per cent. The clinical and differential diagnosis were discussed; also the necropsy findings in 36 cases.

6. Skin and mucosa. Erythema marginatum occurs in from 4 to 15 per cent of rheumatic children and is "specific" for rheumatic fever. It was again described.<sup>435, 540</sup> It usually appears first with an initial attack or a relapse. It may be transitory but may continue long after all other signs of rheumatism have disappeared. Since all cardiac abnormalities in 4 of 13 patients so affected disappeared Perry regarded the erythema as of good prognostic import. [The series of cases seems too small for one to draw definite conclusions.—Ed.]

According to Brim, one may find rheumatic nodules not only in skin but also smaller nodules in the oral and pharyngeal mucosa of many rheumatic patients. These nodules, "a new sign" of active rheumatic fever, varied in size "from pin-point to pin-head" and formed smooth, pink (or white capped), round elevations on the mucosa especially of the anterior faucial pillars and on contiguous tissues. They may occur with or precede other rheumatic manifestations. Their presence was not seasonal but was related to the rheumatic activity.

*Laboratory Data.* 1. Electrocardiograms. The electrocardiographic alterations seen among 100 children who had rheumatic carditis were described in detail and compared with those in 50 cases of congenital heart disease (Drawe, Hafkesbring and Ashman). In general, electrocardio-

grams merely confirm the evidence of rheumatic activity provided by leukocyte counts and sedimentation tests but Massell and Jones noted occasional cases in which long P-R intervals were the only signs of active rheumatism. Fourth lead electrocardiograms have not yet been finally evaluated. In rheumatic children Messeloff and Pomerantz found that Lead IV gave no more data than the three standard leads. Dwan and Shapiro found fourth lead electrocardiograms of no value in cases of congenital heart disease but in cases of rheumatic carditis they amplified and corroborated data from other leads so that myocarditis was diagnosed in 29 per cent of cases by orthodox leads, in 7 per cent more by Lead IV.

2. Sedimentation rates. Studying 163 rheumatic subjects, Massell and Jones noted the comparative value of the sedimentation test and the leukocyte count as indices of rheumatic activity. These tests were helpful, often essential in determining mild activity. In most cases, results of one or both of these tests continued at an elevated level for several weeks to many months after the disease was clinically inactive. In detecting low-grade activity the tests were of equal value but the corrected sedimentation index was the more useful because of inherent errors in making leukocyte counts. Results of one or both tests may be normal in the presence of active rheumatism. In 58 of 163 cases the sedimentation rate remained elevated longer than the leukocyte count; in 55 the reverse was true; in 50 cases both tests became normal simultaneously. Rates may become elevated [but not always.—Ed.] and remain elevated for as long as three weeks after upper respiratory infections or tonsillectomy; hence, elevated rates within three weeks of these events do not necessarily indicate active rheumatism. In conclusion, continued leukocytosis or repeatedly rapid corrected sedimentation indices should, in rheumatic patients, be considered indicative of active subclinical disease in the absence of other cause for their abnormality.

3. Blood counts. An arbitrary level of 10,000 leukocytes per cu. mm. was considered the upper limit of normal by Massell and Jones; in the convalescent stage of rheumatic fever counts were usually not over 12,000 to 14,000. Rae's interesting case of rheumatic fever with leukocytosis (76,000) due to coronary thrombosis was noted. Gwynn reported a case of macrocytic anemia due to fatal, fulminating rheumatic fever.

*Relationship of Rheumatic Fever to Other Diseases.* 1. To congenital heart disease. Evans found no relationship between acute rheumatism of mothers before or during pregnancy, or of fathers, and the congenital heart disease of 30 children.

2. To subacute bacterial endocarditis. Gross and Fried studied the hearts in 70 cases of acute or subacute bacterial endocarditis. Previous rheumatism had affected 75 per cent of them; certain histologic stigmata indicated those cases in which bacterial endocarditis was superimposed on rheumatic carditis. Rheumatic activity was not a necessary precursor of bacterial endocarditis. Aschoff bodies were found in about 30 per cent of the cases of superimposed endocarditis but in some cases the rheumatism

was reactivated by the superimposed bacterial endocarditis rather than vice versa. Eosinophilic necrosis of valve closure lines seemed to predispose to bacterial implantation. Since this is seen more often in acute rheumatism, rheumatic hearts are more susceptible to bacterial endocarditis. Vascularization of valves played no significant rôle. Kinsella noted points of similarity in the pathology of *late* rheumatic valvulitis and of bacterial endocarditis but the *earliest* cellular reactions of rheumatic valvulitis were distinctive; hence, bacterial endocarditis is not an inherent part of rheumatic valvulitis.

3. To chorea. This will be discussed under the heading "chorea."

4. To atrophic arthritis. This will be discussed under "atrophic arthritis."

5. To erythema nodosum. According to Keil, there are four theories concerning the etiology of erythema nodosum: that it is (a) a specific disease; this is the attitude of many dermatologists; (b) tuberculous; this is held by many pediatricians; (c) rheumatic, probably streptococcal; this is the view of many internists; (d) a nonspecific toxic reaction to different causes. Keil summarized the evidence for and against its rheumatic origin. In favor of a close relationship of the two were the fact that it is often associated with sore throat and joint pains. Facts which do not support a relationship are as follows: there is no "true rheumatic throat"; many nonrheumatic infections are accompanied by sore throats; the joint effusions and severe degrees of pain seen in rheumatic fever rarely occur in erythema nodosum; in erythema nodosum carditis, significant electrocardiographic changes, chorea, subcutaneous nodules and pleurisy practically never occur, and salicylates are of no curative value; finally the skin reaction in erythema nodosum is clinically different from that ever seen in true rheumatic fever. Therefore there is no sound evidence that erythema nodosum is rheumatic: "It will not do to label cases of erythema nodosum as tuberculous when the tuberculin test is positive, and as rheumatic when the test is negative."

Erythema nodosum is a nonspecific reaction of skin to a variety of bacterial, toxic or chemical agents; so concluded Spink after a survey of 143 cases and a review of the literature. In Spink's cases the highest incidence was among females 20 to 29 years of age. The disease may accompany tuberculosis (especially in children), hemolytic streptococcal infections and rheumatic fever; lesions similar to it were produced by injections of tuberculin, or of streptococcal nucleoprotein, autogenous or otherwise. To Spink a relationship to streptococcal infections was more evident than one to tuberculosis.

*Differential Diagnosis.* Rheumatic fever is one of the most protean of all diseases; hence, it is unfortunate that there is no clinical sign or laboratory test pathognomonic of the disease.<sup>174, 557</sup> Some of the difficulties of distinguishing it from gonorrheal or acute atrophic arthritis were illustrated (Wainwright and Janeway).

*Course, Prognosis, End Results.* Emphasizing the chronicity of the disease, Sherwood warned that in an acute attack one should expect the fever to last for days, tachycardia and leukocytosis for weeks, the altered sedimentation rates and electrocardiograms for 2 to 12 months, anemia and loss of weight for four months and more. Current data again demonstrated the great tendency to recurrences. Of the 488 rheumatic children studied by Roth, Lingg, and Whittemore, 68 per cent had at least one recurrence during the observation period of 8 years, 40 per cent had two or more; some had three to five; a few had six or more; of the recurrences, 73 per cent appeared within three years of the initial attack. Recurrences affected those who first developed carditis or chorea more often than those first affected by polyarthritis alone or with carditis. Relapses within one year affected 18 per cent of the 141 Chinese cases<sup>107</sup>; over 10 years elapsed between recurrences in 11 cases. Wilson also noted long (7 years) spontaneous remissions, a point to remember in evaluating any treatment. Recurrences were much less frequent among those who had attained puberty (13 per cent affected) than among those who had not (66 per cent affected).

Factors related to pregnancy which tend to precipitate cardiac failure among rheumatic women were: increases in body weight, blood volume and basal metabolic rate; the high diaphragmatic position which lessens pulmonary volume and excursion and distorts heart and great vessels, and the care of the child after birth (Hepburn). Indications for permitting or terminating pregnancy among rheumatic women were detailed. Various factors must be considered, not only the apparent functional cardiac ability, and each case must be decided individually. Among 5366 pregnant women Lamb found organic heart disease in 110 (2.1 per cent); in 102 of them, of rheumatic origin. Heart failure during pregnancy affected more than 50 per cent of those with active rheumatism.

Of 337 patients, 112 (33 per cent) died during Wilson's 20 year period of observation. Carditis practically always developed; in 85 per cent of them before the age of 17 years; the average age at death was 12.6 years. Aside from active carditis the type of rheumatic manifestation first noted carried no prognostic significance. Wallace stated: "It is a solemn thought that 25 per cent of all rheumatic children die from heart disease before they leave school and a further 30 per cent are crippled for life."

*Etiology and Pathogenesis.* No new theories or important variations of old theories were entertained.

Factor of infection. 1. Upper respiratory tract infection. The exact rôle of tonsillar or pharyngeal infections remains uncertain. Among Maddox's 428 hospitalized rheumatic children 102 had sore throats one or two weeks prior to the onset of their acute rheumatism, but in the country sore throats were as frequent among nonrheumatic as among rheumatic children. Sharp and John attempted to determine the significance of the lowered incidence of rheumatic fever and of hemolytic streptococcal sore throats in Galveston, as compared to Chicago. A definite seasonal drop in strepto-



coccal carriage in throats was noted and was lowest in warm weather. Hemolytic streptococci were present in 42 per cent of 908 throat cultures made between October and May, in only 13 per cent of 251 cultures made between June and September. The southern climate reduces, but does not eradicate, tonsillitis. However, throats became sterile of streptococci irrespective of season, and Sharp and John could not conclude that a reduction in oral streptococci was the agency by which southern climate controls the disease. Although the seasonal decline of rheumatic fever and streptococcal throats in Galveston coincided, the incidence of rheumatic fever and especially of chorea continues to remain low throughout the year and does not parallel the winter rise in pharyngeal infections.

The hemolytic streptococci isolated by Keefer and Spink in cases of tonsillitis preceding rheumatic fever were apparently similar biologically and serologically to those in cases of erysipelas and other human hemolytic streptococcal infections. Yet rheumatic fever did not follow erysipelas once in more than 1400 cases of the latter.

In New York, however, the relation between streptococcal pharyngitis and acute rheumatism seemed distinct to Bradley, who studied 550 persons including patients with active, convalescent, and quiescent rheumatism. At some time, 20 per cent of them carried hemolytic streptococci, usually potentially pathogenic to man, of distinct serologic types which varied from time to time. Family epidemics were caused by a single (but variable) type. Of 14 rheumatic patients affected by hemolytic streptococcal pharyngitis 43 per cent had relapses but none of 31 rheumatic patients who escaped streptococcal pharyngitis and none of nine who developed nonstreptococcal pharyngitis had relapses. "There is nothing haphazard about streptococcal infections." According to Bradley an apparently sporadic case of rheumatic fever is not an isolated event but almost certainly part of a streptococcal epidemic of distinct type. Every case of "tonsillitis" should be considered, not a possible example of chronic endogenous infection, but as a dangerous manifestation of an acute exogenous infection—"epidemic streptococcal fever."

2. Skin tests. To determine whether skin tests might serve to identify causal organisms in rheumatic patients, Traut tested the skin in seven cases of rheumatic fever, six of old rheumatic carditis, nine of "rheumatic pains," 20 of atrophic arthritis; also skin of six nonrheumatic atopic persons and 41 nonrheumatic nonatopic persons; he used bacteria "related" and unrelated to rheumatism. He showed again that "arthritic patients" are especially sensitive to streptococci, particularly hemolytic streptococci, but not to staphylococci or gram-negative bacteria. However, there was no evidence that hemolytic streptococci were "specific"; since the positivity of tests was directly proportional to the content of nonspecific irritant substances, such skin tests are of no etiologic or therapeutic value (Traut).

3. Antifibrinolysins. The presence of antifibrinolysins in a patient's plasma presumably means that he has been a fairly recent victim of hemo-

lytic streptococcal infection (Tillett and Garner 1933). Reputedly most patients with rheumatic fever exhibit antifibrinolysis, those with atrophic arthritis do not. However, Waaler has concluded that the reaction is not specific, and antifibrinolysis does not prove that a hemolytic streptococcal infection has been experienced. The majority of seven cases of rheumatic fever showed definite antifibrinolysis, but some antifibrinolysis was present in 50 per cent of 24 cases of atrophic arthritis, and in some cases of subacute bacterial endocarditis from fecal and green-producing streptococci (but not in five cases of Still's disease). The strength of the reactions varied with the severity of the diseases studied.

4. Precipitin tests. Group A hemolytic streptococci contain three known fractions: (1) a nonspecific nucleoprotein—the P fraction; (2) a carbohydrate or C fraction, regarded as group-specific; (3) a type-specific fraction which is a protein substance called the M fraction. The type-specific fraction of group B hemolytic streptococci is a carbohydrate called the S fraction. The presence of antibodies against the C fraction (anti-C precipitins) suggests, but by no means proves, that a patient has been infected with hemolytic streptococci of the corresponding group. Many patients with rheumatic fever possess anti-C precipitins but so do some normals and some patients with other articular diseases, according to Chasis and McEwen (1936). In an attempt to explain the reason for peculiar cross precipitin reactions, Chasis and McEwen studied reactions obtained with crude C-extracts of hemolytic streptococci of various groups (not just group A) in a variety of diseases as well as in immune rabbit serums. Cross-reactions were obtained, due probably to the presence in these serums of antibodies against a nongroup-specific fraction or radical present in the bacteria and in the C-extracts. Chasis and McEwen concluded that this substance is not the nucleoprotein or P fraction and is probably nonproteic.

[This highly technical report throws doubt on the reliability of precipitin tests done with C extracts and indicates that precipitin tests with a C-extract from only a single group must be interpreted with caution.—Ed.]

5. Complement. The complement titer of normal persons and of 33 patients with nonrheumatic complaints was found by Rachmilowitz and Silberstein to vary between 0.04 and 0.06 c.c. The amount of complement in blood was found to be low in active rheumatic fever (complement titers 0.10 to 0.25, av. 0.14 c.c. in 14 cases), but normal in inactive rheumatic fever (6 cases) and in acute atrophic arthritis (13 cases). The determination of blood complement may therefore help to differentiate the polyarthritis of acute rheumatic fever and that of acute atrophic arthritis. The blood complement is low in certain allergic diseases; hence, from their results these workers deduced that rheumatic fever is allergic and that atrophic arthritis is not.

[Complement in human serums does not remain constant in amount even for 24 hours. Without much more work these conclusions seem premature.—Ed.]

No new studies on blood cultures, agglutinins or antistreptolysins in rheumatic fever were reported.

**Virus theory.** Older studies on the virus theory of rheumatic fever were unacceptable because the material presumed to be etiologic could not be proved to be infective. In 1935 Schlesinger, Signy and Amies obtained, from rheumatic exudates, bodies morphologically similar to elementary bodies from known viruses. Although they also were unable to prove their infectious nature this work seemed significant because the bodies were specifically agglutinated by serums of rheumatic, but not by that of nonrheumatic, patients. Exudates of nonrheumatic patients also contained similar looking bodies but they were not agglutinated by rheumatic serums. This work has been confirmed and extended by Eagles, Evans, Fisher and Keith. Particles resembling virus bodies were found in various materials in cases not only of rheumatic fever but also of atrophic arthritis and chorea. Only a few particles, unsuitable for agglutination tests, were found in blood, urine, subcutaneous nodules, spinal and ascitic fluid but particles were readily found in pleural, pericardial and synovial exudates and were specifically agglutinated, suggesting that they were true virus bodies. Furthermore, not only were they agglutinated by the serums of patients suffering from the disease from which the suspension was prepared, but there was considerable cross-agglutination within the group of rheumatic diseases, suggesting that rheumatic fever, atrophic arthritis and chorea are very closely related etiologically, at least serologically.

[These studies have aroused considerable interest. The work has been well done but its significance is not established. The infective nature of the bodies remains unproved; in the absence of such proof some consider their agglutination as providing evidence less impressive than the immunologic data which incriminate hemolytic streptococci.—Ed.]

**Protozoan infestation.** According to one writer,<sup>660</sup> acute rheumatism is "due to a protozoan of which the Aschoff body is the encysted form. This protozoan is introduced by the bites of insects in the late summer or the autumn; e.g., harvest bugs or midges." The author claims to have proved "that all cases of acute rheumatism and chorea occur in the children of the acid class, and of this class alone."

[This is a restatement of the writer's previous but uncited work, given here without proof.—Ed.]

**Vitamin deficiency.** Rinehart summarized the work of himself and colleagues (previously reported in these Reviews).

According to him, the concept that vitamin C deficiency may be a factor in the cause of rheumatic fever is based on strong experimental evidence. Lesions essentially similar to those of rheumatic fever were produced experimentally by the combined influence of infection and vitamin C deficiency. The factor of infection is in no sense minimized. The main pathologic changes in both rheumatic fever and scurvy involve connective tissue. The concept would explain the hemorrhagic and other features of rheumatic fever, including its epidemiologic peculiarities. The blood

plasma in rheumatic fever is low in vitamin C. In brief, experimental, clinical, epidemiologic and biochemical studies all point to the possible importance of vitamin C deficiency in the etiology of this disease.

Further evidence that patients with rheumatic fever are deficient in vitamin C was provided by Abbasy, Hill and Harris. Persons on a "minimal-optimum" dose of vitamin C (25 mg. per day per 140 lbs. body weight) excrete about 13 mg. per day per 140 lbs. body weight. The average daily urinary excretion by 107 patients with active rheumatic fever (or with active tuberculosis) was only 9 mg.; by 86 convalescent rheumatic patients, 10 mg.; but by 64 controls well over 13 mg.; all groups receiving well over the minimum standard amount of the vitamin. The "simplest explanation" was that patients with active rheumatic fever obviously need more vitamin C (since they hold it back) than convalescent rheumatics who in turn need more than normals. [This argument is not necessarily sound; nephritics hold back urea but they don't need it.—Ed.] Does this vitamin C deficiency (or vitamin need) cause or result from the disease? These workers concluded that since patients with tuberculosis and other infections also disclose a deficient excretion (symbol of a need or deficiency of vitamin C) the deficiency may be the effect rather than the cause of active rheumatism. Nevertheless, for reasons given, vitamin C therapy in rheumatic fever was advocated.

Race found evidences of deficiency in both vitamins A and C in patients with subacute rheumatism (and other rheumatic diseases as well, especially in atrophic arthritis).

The vitamin A content of serum ranged from 75 to 140 gammas per 100 c.c. in 14 controls, from 15 to 90 gammas in 10 cases of subacute rheumatism (from 10 to 70 in 14 cases of atrophic arthritis, 10 to 120 in 10 cases of fibrositis, 80 in one case of gout, 90 in one case of hypertrophic arthritis). There was a serum deficiency not only in vitamin A but also in carotene, a precursor of vitamin A. In the rheumatic cases the icterus index and the serum bilirubin content were definitely subnormal; however, the chief cause of the low icterus index was not the reduction in serum bilirubin, which was slight, but an associated reduction in other serum pigments—carotene, a precursor of vitamin A, and xanthophylls, which are not precursors of vitamin A.

The median concentration of vitamin C (ascorbic acid) was 1.03 mg. per 100 c.c. plasma in persons on a diet high in vitamin C; 0.62 mg. in those on a diet "sufficient" in vitamin C, but only 0.39 mg. in those with subacute rheumatism (0.38 in atrophic arthritis; 0.36 in fibrositis; 0.41 in hypertrophic arthritis).

[The numbers of cases studied were small but the results were definite and well controlled.—Ed.]

No final conclusions as to significance were made but Race stated: "Although a vitamin C deficiency may produce some symptoms in man that simulate to some extent those occurring in rheumatic diseases, the clinical picture as a whole is quite different, and more conclusive evidence must be

forthcoming before the hypothesis that these diseases may result from a streptococcal infection superimposed on a vitamin C deficiency can be accepted."

*Conclusions on Etiology.* Poynton expressed the belief that juvenile rheumatism arises from streptococcal infection but not from that in any local focus, and held that "it is as rash to call rheumatism an allergic disease as to claim it is a diathesis." Connor reminded us that one attack of scarlet fever confers considerable immunity but an attack of erysipelas or rheumatic fever increases one's liability to other attacks; yet all are presumably due to hemolytic streptococci. In spite of these immunologic differences many agreed that there was strong evidence that rheumatic fever is etiologically related to beta (but not to alpha or gamma) hemolytic streptococci.<sup>130, 557</sup> [The serologic work of many has led to such a conclusion, and Coburn and Pauli (1932 et seq.) and others have noted that the nasopharyngeal infections which precipitate rheumatic fever are mostly due to group A hemolytic streptococci. If this is so why is sulfanilamide (which is so effective against many group A hemolytic streptococci) so ineffective in rheumatic fever? To some (e.g., Cushing) this forms a strong argument against a direct relationship between rheumatic fever and hemolytic streptococci.—Ed.]

### TREATMENT OF RHEUMATIC FEVER

*General Remarks.* General principles in treatment were reviewed.<sup>415, 588, 615</sup> It is most important that the victim and his relatives first understand the fundamental chronicity and seriousness of the disease. Too often treatment fails because of its too brief use rather than because of its inherent inadequacy.<sup>615</sup> Since long (1 to 10 years) spontaneous remissions frequently feature the disease one must not hastily give credit to any therapy which is followed by a relatively short period of relief.<sup>728</sup> The scheme of the London County Council includes provision of special rheumatism units for prolonged hospital treatment, establishment of centers for early diagnosis and supervision of quiescent cases, a system of supervision of patients discharged from hospital units, amelioration of unsatisfactory home conditions and central coördination.<sup>679</sup>

*Rest.* The theme of all was rest, more rest and still more rest for rheumatic patients, especially those with signs of active or impending carditis; rest until all manifestations of active disease disappear and then for at least two or three weeks longer. The ideal treatment of rheumatic carditis would be to stop the heart entirely, to prevent endocardial and myocardial strain until healing occurred. This being impossible, physical and mental rest are imperative; all else is subordinate (Marsh).

To rest and slow the heart some used digitalis when cardiac insufficiency or persistent tachycardia are present.<sup>588, 700</sup> According to Cushing rest over long periods can be overdone. When signs of rheumatic activity cease, graduated activity is in order. Lightwood's scheme was: "(1) patient lying down, one pillow, fed by nurse; (2) two pillows, patient semirecumbent, allowed to feed himself; (3) patient sitting in bed; (4) patient dressed

and allowed on a couch, later walking a few steps; (5) up half time; (6) up all day."

*Salicylates.* These were considered useful and safe by most writers but of limited value by Eason and Carpenter and by Rosenberg who reviewed salicylate therapy briefly. About 30 cases of methyl salicylate poisoning (18 of them fatal) have been reported since 1799. Lawson and Kaiser reported the death of a child with rheumatic fever who took not over 60 grains of salicylates by mouth and had in five days a total of 3 ounces of oil of wintergreen applied to her knees; dyspnea, vomiting, cyanosis, delirium, acidosis and death three days later occurred. At necropsy the heart was "grossly normal."

*Gold.* Results from a "limited trial" of gold salts were disappointing to Sherwood.

*Sulfanilamide.* Marked relief in a few cases of "acute febrile polyarthritis" treated with "prontosil I" was reported from Germany by Veil (1934) and Scheurer (1936). The results of others, however, have been unfavorable. A fatal agranulocytosis affected a 53 year old man with acute rheumatic fever given prontosil album (3 gm. daily for 18 days) by Young. No definite effect was noted by Basman and Perley and by McQuarrie in two cases each, by Hageman in one case, and by Brown and Bannick in an unstated number of cases.

[Attention is called to the current experiences of Swift, Moen and Hirst (1938): to eight patients with rheumatic fever sulfanilamide was given in as large doses as could be tolerated; no beneficial effect was noted, indeed the patients seemed specially susceptible to toxicity therefrom. "The toxic action of sulfanilamide in active rheumatic fever so far outweighs the beneficial therapeutic effect that its administration to patients with this disease does not seem justified."]

*Treatment of Tonsillitis and Nasopharyngitis.* "Without tonsillitis or pharyngitis there would be little if any rheumatism"; this was the view of Lightwood who painted infected tonsils with protargol and gave potassium chlorate by mouth: He further stated, "If tonsils are irrevocably infected they should be removed; the tonsillar glands and a history of sore throats are our best guide." Others agreed that infected tonsils should be removed as soon as possible.<sup>306, 435</sup> Too often they are removed simply because they are large; the size of tonsils is no index of their infection.<sup>211, 435</sup> Tonsillitis and sore throats are by no means a constant symptom of streptococcal nasopharyngitis. Tonsillectomy often fails to prevent recurrences or ameliorate the condition (Cahan). It had no appreciable effect on the acute streptococcal nasopharyngeal infections seen by Bradley.

*Vaccines, Serum.* The value of vaccines remains unproved (Jordan). The immediate effect of serum in 44 cases seemed good to Eason and Carpenter; 30 c.c. of Parke Davis' concentrated antiscarlatinal serum were given intramuscularly and repeated within 36 hours. Patients generally became afebrile in about three weeks. [Untoward reactions occurred very occasionally; to prevent these a few minims of adrenalin solution (1:1000) are now

given with each injection of serum.—Ed.] The effects of serum and salicylate were compared. Serum prevented more relapses, was effective in cases resistant to salicylates but was accompanied by longer fever and occasionally by serum sickness or other reactions. The effects of serum may be partly due to its foreign protein content, but more relapses occurred in a few cases in which treatment was by similar amounts of foreign protein without serum.

[This report is interesting but serum therapy must be evaluated in a larger series of cases observed for a longer time.—Ed.]

*Transfusions.* Rosenberg reported the case of a nine year old boy in his sixth attack who after 12 weeks of continuous fever and a persistently high sedimentation rate was given seven transfusions of blood (each 100 c.c.). The sedimentation rate and fever then dropped progressively and the patient improved decidedly. Similar results were noted in the literature. [The result would have been more impressive had not slight clinical improvement and a slight drop in temperature (but not in the sedimentation rate) been noted before the first transfusion. Further observations are desirable.—Ed.]

*Diet and Vitamins.* Although the use of vitamin C produced results "encouraging" to Rinehart (1936), others noted therefrom no reduction in the incidence or severity of the disease.<sup>4</sup> Abbasy, Hill and Harris expressed the belief that vitamin C therapy is "likely to be helpful," and that its prophylactic and therapeutic value should be investigated further. Diets high in calories and excessive in vitamins A, B, C, and D were given by Sadow, Hubbard, and Jones to 31 rheumatic patients for an average of 20 weeks; except for increases of weight no benefits were noted. [However, the group receiving the special diet were sicker than the 25 in the control group.—Ed.] Rinehart's answer to such results follows: Too much must not be expected of vitamin C therapy as we are dealing with something much more complex than a simple deficiency. If vitamin C deficiency prepares the soil for an infection to produce rheumatism, the deficiency is only contributory. Valvular deformities would never be anatomically corrected by vitamin C therapy. The most that could be achieved would be restoration of tissues to a state in which they could resist the injurious influence of infection. Prolonged studies are necessary to determine its prophylactic and therapeutic value.

*Fever Therapy.* This was considered valuable by Simmons. Of nine cases of acute rheumatic fever with active endocarditis six became inactive in an average of 24 days following an average of five treatments. Three cases of endocarditis and chorea became inactive in an average of 46 days after an average of nine treatments (2.5 to 4 hrs. at 103 to 105° F.). [The cases have not been observed long enough to note the effect of treatment on prevention of recurrences and complications.—Ed.]

*Special Treatment for the Heart.* Rothbart gave repeated intravenous injections of 15 to 20 per cent dextrose to "improve the heart's nutrition." It "did no harm" and seemed to relieve the acute abdominal pain and vomiting associated with acute pericarditis. Roentgen therapy seemed

valuable to Levy and Golden who observed during a period of 11.5 years 48 patients so treated. Cases with low grade activity and no congestive failure were most benefited. The therapy relieved cardiac pain in those without aortic insufficiency, produced no harmful effect but some unpleasant radiation reactions. Cardiac failure can often be prevented or postponed by attention to its premonitory signs: fatigue and limitation of activity through breathlessness (Felter). Attention to heart size is more important than that to heart sounds.

*Institutional Care and Climate.* Living in the South several months hastens recovery from individual attacks but when patients return North their future course is not significantly altered. To be helped materially children should spend their entire childhood, at least until puberty, in the South; unfortunately this is impracticable on a large scale (Hedley, Wilson). Although favoring convalescent cardiac hospitals and vocational guidance in schools, Hedley did not recommend special schools or classes for rheumatic children: "The psychological effect is bad. It is better to enroll them in schools near their homes and to limit their activities according to their functional capacity." Others favored rheumatic colonies and schools near all large towns and cities.<sup>698</sup>

*Prophylaxis.* Recommended were isolation of rheumatic children with active disease from intimate contact with other children but particularly from persons with respiratory infections<sup>306, 415</sup>; after-care so that children are not returned to the same conditions of poverty and overcrowding which fostered their disease,<sup>698</sup> governmental grants of adequate food to impoverished children<sup>64</sup>; a wider use of prophylactic schemes like that of the London County Council.<sup>164</sup>

#### SYDENHAM'S CHOREA

As in previous years, the reported incidence of chorea with rheumatic fever varied markedly—from 1.5 per cent to 44 per cent. [Is this a true difference in incidence or a matter of proper recognition?—Ed.] In Australia "cho-reiform motions" affected only 1.5 per cent of Maddox' 428 juvenile patients with rheumatic fever. Chorea affected 8.5 per cent of Chinese patients,<sup>107</sup> 25 per cent of 488 patients with juvenile carditis in New York,<sup>587</sup> 29 per cent of 73 rheumatic patients in Boston<sup>447</sup> and was the first symptom of 44 per cent of 516 rheumatic children in Edinburgh.<sup>698</sup> Chorea was 33 times more frequent in Chicago than in Galveston.<sup>611</sup> The likelihood of patients with chorea developing progressive rheumatic symptoms and carditis is not clearly established. Warner's patients with chorea seemed to escape carditis more frequently than those with other rheumatic symptoms. Among Wallace's patients, those whose first rheumatic symptom was chorea developed rheumatic recurrences less often than those whose first symptoms were from joints or heart. However, in Wilson's group the type of rheumatic symptoms first noted (aside from carditis) carried no prognostic significance.



*Relationship to Rheumatic Fever.* Although many rheumatic patients develop chorea and many choreic patients develop carditis and other rheumatic symptoms the connection between chorea and rheumatism has not been settled. Some regard chorea as (1) a symptom of rheumatic fever (e.g., Jones and Bland, 1935); (2) a symptom of several diseases, among them rheumatic fever; (3) an independent disease which may accompany rheumatic fever. The first view was supported by three reports.<sup>523, 587, 724</sup> Among 112 choreic children, Parish, Taran and Starr noted the development of carditis in 53 per cent of 78 cases of "pure chorea" (onset with no other rheumatic symptom), and in 76 per cent of 34 "mixed cases" (chorea with other rheumatic symptoms). Esophagrams showed the incidence of carditis to be even more nearly equal in the two groups. Doubtless nonrheumatic irritants may initiate choreiform symptoms in certain cases, but since the incidence of carditis in pure chorea is almost as high as that among children with the rheumatic diathesis, it was assumed that chorea is of rheumatic origin. Williams' conclusion was similar: Among 142 choreic children were 41 (29 per cent) with, and 101 without, evidences of rheumatic fever. Of 66 choreic children especially studied, 62 per cent had pure chorea, 29 per cent had chorea with carditis, and 9 per cent had chorea but later carditis developed. Recurrences of chorea did not predispose to carditis. It was impossible to tell which choreic child would have rheumatic complications. Chorea frequently accompanied rheumatic carditis, and polyarthritis and carditis were "not uncommon complications" of primary chorea in cases seen by Roth, Lingg and Whittemore but they believed that valvulitis associated with chorea is not due to chorea but to accompanying or intercurrent episodes of polyarthritis and carditis.

The view that chorea and rheumatism are independent was upheld by Coburn and Moore. Of 114 choreic patients studied 2 to 10 years, 30 per cent had no (other) evidence of rheumatism. Of another group of 137 cases of chorea, in approximately half chorea developed repeatedly but no evidence of rheumatism; sedimentation rates and leukocyte counts were persistently normal, there was no familial rheumatism and attacks were precipitated by psychic trauma, not by respiratory infections. Of the other half (68 cases) chorea developed in 29 during quiescent, and in 39 during active, rheumatism. Thus "half of all cases of chorea in New York may occur in individuals not susceptible to rheumatic fever." The physiologic background prerequisite to the development of chorea "may be prepared by a number of abnormal conditions but is especially well prepared by the rheumatic state. This accounts for its frequency in rheumatic patients." But the factor which initiates chorea can be independent of rheumatism and "chorea is not pathognomonic of active rheumatism." A case of Dawson-Walker and Brewis illustrated this point: A boy, aged 12 years, had severe diphtheria, then bulbar paralysis, Sydenham's chorea and multiple peripheral neuritis "as the result of the action of diphtheria toxin on the basal ganglia and higher centers." No previous rheumatic history or manifestations were apparent.

*Other Clinical Data.* Sex incidence for girls was 56 per cent in one group<sup>724</sup>; 53 per cent in another.<sup>523</sup> Of Williams' cases, fever was absent in 62 per cent, slight in 17 per cent, definite (100° F. or more) in 21 per cent. It was again emphasized that in chorea sedimentation rates are normal unless other rheumatic signs are present.<sup>18, 123, 224, 724</sup> Evans noted obesity complicating juvenile chorea and considered it "post encephalitic obesity, possibly with degeneration in the suprapituitary region."

*Treatment.* The use of calcium gluconate, grains 15, and acetylsalicylic acid, grains 10, every four hours seemed to shorten the chorea in 23 of Pearson's cases but the idea of Mutch (1934) that chorea was due to a low concentration of calcium in spinal fluid, correction of which cured chorea, was not confirmed.

Fever therapy continues to be the method of choice in chorea. Although there is no definite evidence that it influences the subsequent appearance of carditis; results, generally excellent, were reported in about 80 cases. Barnacle, Ewalt, and Ebaugh treated 45 patients, 19 (42 per cent) with active carditis. Prompt recovery occurred in 37 cases, marked improvement in eight. At the follow-up (two years or less) of 40 patients, 36 were still well, four had had recurrences. Carditis was not a contraindication, indeed it was benefited. Of those with carditis the immediate effect was recovery therefrom in seven, improvement in eight, none in four; late effects in 12 were six cured, six improved. Patients received a total of 40 hours (av.) of fever during (av.) 13 treatments. Of 11 patients treated by Schnabel and Fetter eight were promptly cured, two markedly improved, and one boy died of uncontrollable fever after one treatment. Results were often excellent after only one or two treatments but three to five were usually given. At the follow-up (2 to 7.5 mos. later) eight were well, two had had mild recurrences.

All of five patients given one to 11 sessions of fever by Kendall and Simpson were promptly cured and there were no recurrences. Mitral murmurs present in three cases disappeared. Of eight patients treated by Spekter and McBryde, five obtained good results; one moderately good results and two, indefinite results. Three choreic patients with active carditis received nine (av.) sessions of fever from Simmons; all became free of chorea, fever and pain within 46 days. An excellent result from one session of fever (5 hours at 105° F.) was noted in one case of Solomon and Kopp. A patient with chorea and active carditis received five sessions (5 hours at 105 to 106° F.): Williams<sup>724</sup> stated that the signs of carditis (tachycardia, first degree heart block) disappeared six days after the last session of fever. Most of these workers used artificial fever, each session being 2.5 to 3 or 4 hours at 105 to 106° F., sometimes at 104 to 105° F. (rectal). Some gave five hours of fever at 40 to 40.5° C.<sup>641</sup> Humphris used fever from short waves. Rothbart had "singular success" from 10 to 15 daily intravenous injections of triple typhoid vaccine. The latter was also considered by Spekter and McBryde easier to give and as good as

artificial fever. Long (two to three hours) hot tub baths cured two of three patients of Lowenburg and Nemser. The water was first heated to 85 to 95° F.; then to 105 to 110°; the patients' temperatures rose to 103 to 104° F. An average of 12 daily baths was given. One patient who had valvulitis noted no ill effects.

One death from artificial fever and one from fever induced by typhoid vaccine occurred. After only 1.5 hours of fever (first session) a 12 year old boy had shock and uncontrollable fever and died in 17 hours. Carditis was not noted clinically or at necropsy; cerebral edema and venous congestion were found.<sup>509</sup> Parish, Taran and Starr treated 112 children with rest, warm baths, sedatives and, in 20 cases, typhoid vaccine: 105 were improved, three unimproved and four died; of the latter, three died in acute decompensation, one child died in the course of uncontrollable fever (110° F.) shortly after the fourth injection of typhoid vaccine.

### CHRONIC ARTHRITIS: THE GREAT TYPES

*Clinical Relationship.* No interest was exhibited in arguing the relationship of the two great types of chronic arthritis, atrophic and hypertrophic, one to the other. Without discussion, most writers treated them as different diseases. Others<sup>473, 530</sup> still balked at a final separation and expressed the belief that the two may have certain "basal features" or "many etiologic factors in common" even though their clinical and pathologic differences are obvious. The majority made no place for a third type but regarded "infective arthritis" as synonymous with, or at most a clinical variety of, atrophic (rheumatoid) arthritis. Others considered "infective arthritis" distinct and thus that there are three, not two, great types of chronic arthritis.<sup>160, 604</sup> Crowe summarized the supposed distinction briefly: atrophic arthritis generally affects young women, involves small, rather than large joints, produces characteristic symmetrical swellings, trophic changes, muscle atrophy, and, in roentgenograms, general decalcification of bone with slight loss of cartilage but no bone proliferation or destruction. "Infective arthritis" differs from atrophic arthritis "in nearly every respect"; a generalized disease with joint manifestations, its lesions are not symmetrical; metacarpophalangeal rather than interphalangeal joints are likely to be involved; severe destruction of bone often occurs but not generalized decalcification of bone.

[We cannot subscribe to this distinction.—Ed.]

*Roentgenologic Differences.* The value of roentgenologic differentiation was debated. Roentgenologists are likely to believe that great reliance can be placed on roentgenographic differentiation although it should be correlated with clinical findings.<sup>604</sup> But most rheumatologists do not make the proper use of roentgenography. According to Scott roentgenograms are made "more from curiosity than anything else." No effort is made to standardize position or technic and interpretation is superficial, generally

made by unqualified persons. At least 10 per cent of persons sent to a roentgenologist as having "rheumatism" do not have that disease but have sarcoma, metastatic carcinoma, Paget's disease, Charcot's disease, enchondroma, renal disease, etc. Buckley<sup>85</sup> was fearful lest "the cursory examination of an x-ray picture may displace the clinical study which is the most important." "The most skilled interpretation of a radiograph is of no service if divorced from the clinical study of the case as a whole, and differential diagnosis based on trifling differences in roentgen-ray appearances may only lead to error in prognosis and treatment." He concluded that in a study of atrophic arthritis "x-rays are of little importance as a guide to the management of a case."

The rôle of roentgenology in chronic arthritis was critically appraised by a roentgenologist, Fineman, who studied many types of arthritis in connection with clinical data. In "typical cases," in which articular changes are advanced enough for features to be characteristic, roentgenograms may be adequate for a tentative roentgenologic diagnosis of atrophic or of hypertrophic arthritis but very often the roentgenologist cannot distinguish between them without great difficulty, if at all. In the various types of arthritis changes depend on the duration of the disease, joints involved, age of the patient and many other factors. Most roentgenologists currently believe that articular changes due to trauma or specific infections, or due to neuropathic, endocrine, metabolic and chemical disturbances, are not sufficiently pathognomonic for an etiologic roentgenologic diagnosis. "In chronic arthritis of every type the roentgenologist is often faced with insuperable difficulties when he attempts etiologic classification solely on the basis of roentgen findings. The pitfalls are numerous and mistakes in diagnosis are frequent." The final diagnosis should be made only after consultation with the clinician and correlation of all known facts. "In the final analysis the clinician must still, in most instances, rely on his clinical judgment for the etiologic classification of chronic arthritis." However, the roentgenologist can be of distinct aid in demonstrating focal infection, and Fineman outlined the roentgenologic features indicative of infection in various foci.

*Constitutional Relationships.* Booth studied the personality of 43 patients with chronic arthritis, their childhood problems and development, the psychologic problems and traumatic influences which closely antedated their arthritis, results of the Rorschach test, etc. A close etiologic relationship between psychologic disturbances and the onset, localization and progression of arthritis was seen.

[Having stated that of the patients studied 25 had rheumatoid, and 18 had osteoarthritis Booth thereafter ignored the distinction completely and gave no analysis of the psychologic differences of either type separately. No attempt was made to study a control series of cases of one or several other incapacitating chronic diseases. It seems to us the writer went to extremes in developing his thesis. If the proper significance is to be attached to psychological factors in arthritis such studies should be made with the closest coöperation between the internist and the psychiatrist.—Ed.]

## ATROPHIC (RHEUMATOID, PROLIFERATIVE, INFECTIOUS) ARTHRITIS.

*Incidence: Race, Age.* American Indians of the Southwest are not exempt from the disease: Among 2700 adult Pima Indians who had spent their entire lives on the Arizona Reservation two had atrophic arthritis (Dunham and Montross). Some hold that atrophic and hypertrophic arthritis are different expressions of the same disease at different ages: The chief objection to this idea is that atrophic arthritis, similar in all respects to that of young persons, may affect persons 60 to 70 years old.<sup>473</sup>

*Subtypes.* The British National Committee subdivided rheumatoid arthritis into (1) rheumatoid arthritis with associated factors (i.e. focal infection); (2) rheumatoid arthritis with no known associated factors. [We have discussed this in previous Reviews.—Ed.] Cecil considers this distinction "intriguing but unjustified" since both present about the same pathologic, clinical and immunologic responses and only "differ" as to whether or not a focus of infection is found (a point of debatable significance). But Warren, Hinton and Bauer separated "typical" from "atypical rheumatoid arthritis" by the absence in the latter of the characteristic history, habitus and physical conditions usually seen in the former. Features presumably distinctive of the atypical form were its presence in sthenic rather than asthenic persons, generally sudden onset after infection without other prodromes, frequency of obvious foci, asymmetrical involvement often of large joints, frequent response to salicylates and long remissions; hence, a better immediate prognosis.

This is the distinction made by those who separate "infective arthritis" definitely from atrophic or (ordinary) rheumatoid arthritis. Crowe considered true rheumatoid arthritis a rare disease, present in only 254 of 2704 cases recently seen, the other 1019 being of osteo-arthritis. [This seems to indicate either a practice specialized among elderly arthritics or else a differentiation not similar to that of most American clinicians.—Ed.] Scott also differentiated, roentgenologically, "infective arthritis" from rheumatoid arthritis but his differentiation seems arbitrary and ambiguous in the light of his case 2. Roentgenograms of a patient with the "typical clinical picture of rheumatoid arthritis" (spindle joints, etc.) disclosed no generalized disturbance of bone calcium. Hence, Scott called it "infective arthritis, not rheumatoid." But signs of "toxic thyroid" were later disclosed "and with appropriate treatment complete recovery resulted."

[The propriety of applying the term "infective arthritis" to a condition supposedly due to thyroid toxicity seems questionable.—Ed.]

*Clinical Data: Symptoms, Course, Prognosis.* The necessity of establishing definite criteria for the identification of atrophic arthritis was stressed by Cecil whose criteria follow: 1. Data considered essential were fusiform fingers, the most characteristic early lesion, and polyarticular involvement. 2. Data considered very helpful in diagnosis, and usually or often but not always present were positive agglutination tests for hemolytic streptococci,

subcutaneous nodules (larger and more persistent than those of rheumatic fever) the pathologic reactions of which nodules are "almost pathognomonic of the disease," and demonstration of the typical pathologic change of articular tissue removed at biopsy when possible. 3. Data considered non-essential, frequently present but not consistently enough to be reliable, were vasomotor disturbances, muscle and skin atrophy, presence of antistreptolysins and precipitins, rapid sedimentation rate (not specific) and "characteristic" roentgenographic changes (absent in early stages).

Subcutaneous nodules, varying greatly in size, accompany the disease in 20 to 30 per cent of cases (rarely or never in hypertrophic arthritis) according to Miller, but in only 4 to 5 per cent of cases according to Cecil. They usually develop at pressure points—near an elbow over the ulna, when the ulna is used to bear weight, because the wrist on that side is arthritic; over the occiput or spine of thin, bedridden persons.<sup>133</sup> Cohen noted a point frequently mentioned but inadequately studied: The increased pains which precede storms usually disappear when the rain actually begins. Crowe discussed the variability of pain: Regardless of etiology, symptoms are due to reaction of joint tissues; the greater the reaction, as a rule the more the pain. "In conditions of poor health or of illness joint tissue reaction is less, [not entirely clear as to meaning or as to how it is demonstrated.—Ed.] hence the pain also is less, and in fact during an intercurrent illness such as influenza, swellings and pains may for the time disappear altogether."

Data on the course and prognosis of the disease among children are meager; hence those of Colver are of special interest.

Sixty-nine children were studied "since the war"; 60 per cent were girls. Age of onset was: less than one year in two cases; at the age of one year in eight; two years in 14; three years in six; four years in 12; five years in four; six years in four; seven years in four; eight years in five; nine years in two; 10 years in six. [The chart is not clear; this totals to only 67, not 69 cases.—Ed.] Of 49 patients followed (for an unstated time) 12 were dead, 18 had active and 19 had quiescent arthritis. The disease was apparently self-limiting, lasting an average of nearly five years; never more than seven years. The disease of 19 was "cured" or quiescent; of these, eight were crippled in one to four joints; four were practically cured, having only occasional slight discomfort on full motion; seven were completely cured. Thus, complete recovery was frequent among those whose disease lasted two to three years but when it lasted more than three years recovery was never complete. It can be expected that "approximately one in four recover completely." [This is not the experience of some of us.—Ed.] Gross crippling was uncommon; all but two patients could earn a livelihood; all but one could walk. In no case did symptoms recur after 18 months of quiescence.

In the course of the active disease, a mid-diastolic murmur developed in one case; one patient had adherent pericarditis; "none of the old cases" had valvulitis. "There is no period in life when the onset of rheumatoid arthritis may not be associated with glandular enlargement" but adenopathy and splenomegaly were common in this group. Among patients affected in the first four years of life, adenopathy was the rule (present in 80 per cent) rather than the exception. In the older cases it was progressively rarer (present in 33 per cent). It had no influence on prognosis. Exacerbations of arthritis were frequently related to nasopharyngitis but removal of foci did not seem to influence the prognosis. The high mortality was remarkable:

Of the 42 children who developed the disease in the first five years of life 12 (29 per cent) died, usually within three years. No deaths occurred among those first affected after five years of age and, if children, no matter how young, when first affected, survived three years of the disease, practically none of them died of it thereafter. Five of the 12 deaths occurred in hospital and were due to extreme progressive emaciation and anemia, terminal lesions being hemolytic streptococcal septicemia in two cases, renal calculus with infection in one, amyloidosis and pericarditis in one, unknown (but pericardial adhesions present) in one. Pneumonia was the cited (but uncertified) cause of death of most of the seven patients who died at home.

The "criteria of cure" noted by Cecil and by Colver were: Partial or complete functional restitution of joints (except for residual thickening or limitation due to ankylosis); absence of pain, swelling, exhaustion, leukocytosis or anemia and absence of an altered sedimentation rate and of specific agglutinins for hemolytic streptococci for at least two years.

*Unusual Clinical Features; Effects of Jaundice.* Further observations on the inactivating effect of spontaneous jaundice on atrophic arthritis and on primary fibrositis were reported by Hench. Thompson and Wyatt noted the preliminary effects of "induced jaundice" (experimental hyperbilirubinemia) on atrophic arthritis.

[Since these 1937 reports were only in abstract they will not be discussed here: the full reports (1938) will be discussed in the next Review.—Ed.]

In this connection, a case reported by Boros is of great interest: In 1935 a young man was seen who had had ragweed hay fever with severe asthma every August for eight to nine years so badly that it became an "intolerable burden." Desensitization had given no relief. For an unstated time he had had "rheumatic pains" in a leg for which, during 10 months, he consumed 100 cinchophen tablets, never more than three a week. These gave "no actual freedom from pain." He then (August 1935) developed anorexia, malaise and weakness, and shortly thereafter (date not stated) jaundice but no pruritus. Then a "momentous thing" happened; as noted, the entire train of symptoms from which he had been suffering over so many years ceased promptly as jaundice with its attendant hepatic involvement appeared. "During August just preceding the onset of the jaundice the patient had experienced a complete cessation of his hay fever symptoms" and "with the onset of the jaundice all his rheumatic symptoms suddenly cleared up." A year later the [anti-allergic and anti-rheumatic?—Ed.] factors were still operating: He had no hay fever or asthma in August 1936 and even spent two weeks "where the ragweed literally abounded in countless numbers, enjoying his stay in complete happiness and comfort."

[On the basis of his early experiences Hench (1933) considered this phenomenon "relatively specific" for atrophic arthritis and fibrositis but regarded the possibility that the phenomenon might be more basic than an anti-rheumatic one. As he recently stated: "Perhaps the exhibition and application of the phenomenon may be possible in other conditions." The report of Boros seems to strengthen this possibility.—Ed.]

*Atrophic Arthritis with Enlarged Lymph Nodes, Spleen and Liver; Still's Disease.* When atrophic arthritis affects children aged four years or less, almost always it is accompanied by lymphoid hyperplasia. The accompanying condition is seen less often among older children; with increasing rarity among adults.<sup>186</sup> Since articular changes in late Still's disease are similar to those of late atrophic arthritis of adults, many regard

Still's disease as simply juvenile atrophic arthritis.<sup>126</sup> Kauffman noted six cases of adult Still's disease among 2000 cases of atrophic arthritis; all patients were young women affected at least seven months with arthritis. In sequence there appeared enlargement of cervical, epitrochlear, subinguinal and axillary (but practically never submaxillary) lymph nodes, and of spleen and liver, the latter transiently. Biopsy of lymph nodes disclosed hyperplasia and mild infiltration with round cells. Cyclic exacerbations of lymphatic hyperplasia accompanied increased joint pains, fever, and prostration. Associated features were recurrent acute abdominal pain, nausea and rigidity sometimes simulating appendicitis, lasting 24 to 72 hours; also skin reactions (rheumatic nodules, erythematous blotches or acute urticarial lesions), less commonly hemorrhagic conjunctivitis. The cyclic reactions were at times aborted by injections of triple typhoid vaccine "in the first few hours of the attack." The prognosis was that of ordinary atrophic arthritis.

Collins reported two cases of atrophic arthritis affecting adults, with leukopenia, splenomegaly and hepatomegaly and reviewed the literature thereon. The cause of enlargement of the spleen and liver was not determined. The neutrophilic leukopenia probably was the result of premature and excessive destruction of maturing polymorphonuclears rather than of failure of bone marrow. Injections of pentnucleotide were ineffective. Since the arthritis was identical with atrophic arthritis Collins regarded adult Still's disease or "Felty's syndrome" simply as a rare variety of atrophic arthritis.

[So do we.—Ed.]

*Pathology.* 1. Joints. The pathologic reactions in synovial membrane (vascular granulation tissue with focal collections of lymphoid cells) seemed "specific" for this disease to Cecil, but not to Fisher, who regarded them as similar to those in rheumatic fever. In addition to the usual changes (proliferation of synovial cells and of vascular endothelium, focal collections of lymphocytes "in the main perivascular") Fisher found areas of fibrinoid degeneration (first noted in atrophic arthritis by Klinge and Grzimek, 1932) and two changes "not described before"—giant cells of the Aschoff type and sometimes edema of synovial membrane. Collins cited Walker Swift to the effect that the focal lymphocytic collections and synovial proliferations seen in atrophic arthritis sometimes occur in the synovial lining of tendon sheaths in traumatic tenosynovitis.

2. Nodules. Opinions differ as to whether the nodules of atrophic arthritis and those of rheumatic fever are identical. Some (i.e. McEwan 1933, Dawson 1933) believe that they are; others do not. Collins<sup>132</sup> emphasized the differences, rather than the similarities, in the nodules of atrophic arthritis and rheumatic fever: According to Collins the differences are more striking than the similarities, therefore the nodules must be basically different.

The early nodules are similar in both diseases but developmental differences appear. Both reveal fibrinoid degeneration, proliferation of young fibrous and connec-



tive tissue cells, vascular proliferation and peculiar vascular changes. In nodules of rheumatic fever there is always more vascular proliferation and more polymorphonuclear leukocytic invasion and the nodule tends to organization and replacement by normal fibrous tissue after a few months. In arthritic nodules the early size and spread of necrosis is far greater than in the others: "The large spreading focus of necrosis with its deep wall of fibroblasts is characteristic only of the rheumatoid arthritis nodule as is its later development into a fluid-containing cyst with connective tissue lining." Another fundamental difference: Alteration of original collagen is supposedly the earliest change in nodules of rheumatic fever but in those of arthritis connective tissue proliferation precedes the degeneration which subsequently takes place in the new tissue. [One of us, M. H. D., cannot agree with this.—Ed.] Clinical differences also exist: In rheumatic fever nodules occur also in skin, in tendinous expansions and in other sites less exposed to trauma, are nearly always multiple, never attain the size of those in arthritis and disappear with the acute attacks; those in arthritis appear at points of trauma but not in skin, small ones may undergo resolution and cicatrization and disappear, but many persist for years with permanent, bulky scars. The arthritis nodules are different also from those caused by trauma alone.

*Röntgenograms.* The characteristic features and difficulties in diagnosis were outlined by Fineman.

*Laboratory data.* The relative value of laboratory data in diagnosis and in estimating activity and prognosis were studied by Short, Dienes and Bauer and by Kersley.<sup>372</sup>

1. Blood counts. Total and routine differential leukocyte counts are of little help in following the course of atrophic arthritis. When the disease is acute and febrile, leukocytosis may occur; in chronic cases the count is normal or low. Often polymorphonucleosis is present early; later, neutropenia with relative lymphocytosis. To study activity and prognosis, Arneth-Schilling counts of filamented and nonfilamented leukocytes are useful: In active atrophic arthritis immature (nonfilamented) cells are increased. In 35 cases 100 tests were done; 87 per cent were positive (young cells more than 8 per cent). They were positive in 65 per cent of patients less than one year old; in 93 per cent of older patients (Short, Dienes, Bauer). Kersley's results were variable: The Arneth count was sometimes high, sometimes low; the shift was usually to the left but sometimes to the right (details not given).

2. Sedimentation rate. This was again considered the most useful test in making an early differential diagnosis and in estimating activity of the disease. Using the Rourke-Ernstene method and correcting for anemia, Short, Dienes, and Bauer noted elevated rates in 92 per cent of 154 tests on 49 patients; rates were rapid in 79 per cent of tests on patients less than one year old, on 96 per cent of older patients. Kersley noted persistently normal rates in a few cases apparently similar to atrophic arthritis. He considered wide-bore tubes more delicate and accurate than narrow tubes and the capillary methods "almost useless." Using the Cutler method, Lautman noted elevated rates (more than 10 mm. in 1 hr.) in all of 118 cases.

Those interested in the numerous physicochemical factors which influence the rates are referred to several instructive papers.<sup>55, 76, 418, 431, 582, 731, 744, 751</sup> Wintrobe recommended reporting both corrected and uncorrected rates; sometimes uncorrected rates are more significant. New methods were suggested.<sup>128, 193</sup> Because rates by ordinary methods are "of very slight value and should be discarded," Crowe recommended the differential sedimentation test of Coke.<sup>128</sup> Bannick, Gregg and Guernsey recommended the simplest technic (tall Westergren tubes) so that the test will be widely used. Mental allowance should be made for the fact that anemia accelerates rates "but a routine correction for anemia in each case is unnecessary."

[Some of us cannot agree.—Ed.]

3. Vernes test. In atrophic arthritis the result of the Vernes resorcinol test on serum is reputedly generally abnormal. Short, Dienes and Bauer found it abnormal in only 58 per cent of 49 cases and less useful than other tests.

4. Saline absorption test. The test was abnormal in 4 of 14 cases; Kersley considered it valueless.

5. Plasma pigments; other blood studies. Race noted that the plasma pigments, bilirubin and carotene, were slightly reduced in atrophic arthritis. The blood glutathione is normal even though the cystine content of nails may be low. Of 60 patients with atrophic arthritis increases were found in blood creatinine in 23 per cent; in urine creatinine in 7 per cent; in blood creatine in 3 per cent; in urine creatine in 30 per cent (Moreno). No interpretation was offered.

6. Glucose tolerance tests. Results of tests were abnormal in only five of Kersley's 47 cases. There was no relation between the height of the curve and the sedimentation rates. Various explanations of the abnormal glucose tolerance tests in arthritis and other chronic diseases have been offered: That these results are due to, (a) disturbances of pancreatic function; (b) circulatory disturbances, slowing removal of sugar from blood (Pemberton, 1920); (c) hepatic dysfunction, the effects of toxemia on liver, not pancreas (Soskin, Allweiss, Mirsky, 1935).

7. Liver function tests. Using the azorubin S excretion test, Rawls, Weiss and Collins found hepatic dysfunction in 55 per cent of 100 cases of atrophic arthritis; dysfunction was present in severe cases more often than in mild cases (73 per cent of severe cases; 48 per cent of moderately severe cases, 25 per cent of mild cases). In most cases showing dysfunction the total serum protein was slightly low; the albumin and globulin ratio reversed.

[This report is interesting but difficult to evaluate. The test used is not one commonly employed. Results with it were not compared to those with standard liver function tests and controls were not studied, except a few cases of osteo-arthritis. The work should be extended.—Ed.]

## ETIOLOGY AND PATHOGENESIS OF ATROPHIC ARTHRITIS

*Factors of Infection.* 1. Foci. No new work of significance was done on the relation of foci of infection to atrophic arthritis. Many writers made

the usual general comments and incriminated this or that focus. These will be noted briefly under "management of foci." Foci, generally in throat or pharynx, were present in 58 per cent of Thompson's 343 cases; bacteria most often present were hemolytic streptococci. [No further data were given.—Ed.] According to Heyd "One may reasonably expect that approximately 5 per cent of patients with chronic arthritis have a disease of the gallbladder and that, in these 5 per cent, either the primary or secondary mechanism for arthritis resides in the gallbladder." [No statistical, bacteriologic or clinical proof was offered. Others have noted cholecystitis in 4.5 to 6 per cent of cases of atrophic arthritis (Hartung and Steinbrocker, 1932; Judd and Hench, 1933) but this incidence is no higher than that among any general group of patients seen in large hospitals or clinics.—Ed.] Stabler and Pemberton found abnormal amounts (but not types) of bacteria in the stools of 17 patients with "chronic arthritis." Aerobic and micro-aerobic streptococci were found in all stools. According to Dawson the intestines are the natural habitat of certain hemolytic streptococci. Streptococci are ubiquitous and their presence in nasopharynx, intestines and on skin is "entirely without significance." From a study of 4000 "arthritis patients" (types unstated) Barrows concluded that important pelvic foci were present in 6 to 10 per cent. Among 1000 patients with "arthritis," genito-urinary foci were found by Taylor in 65 per cent of 400 who admitted a previous "genito-urinary history"; in only 5 per cent of those who did not. Sometimes "genito-urinary infection can be the sole cause of arthritis."

[We see no value in discussing these papers in detail. The protagonists and antagonists of the theory of focal infection in arthritis have reached an impasse where those who believe in it "believe" and those who don't, don't. For the former no new "proof" is needed; for the latter no "new" data are convincing. Until really new and strikingly different data are forthcoming, this impasse will continue.—Ed.]

The pathogen selective culture method (Solis-Cohen) was applied by Crowe to 4181 specimens (urine, feces, vaginal swabs, etc.) in 1390 cases, chiefly arthritic. All types of arthritis gave positive cultures; all seemed to be infective, including osteo-arthritis. Crowe concluded that the method is of great value for isolating special organisms for use in vaccine treatment but that it has very little bearing on the pathology of the disease. Only occasionally did it appear that the microbe isolated was the sole infecting organism. There was, as a rule, "no evidence that the microbe isolated is the direct cause of a chronic rheumatism or arthritis, and any focus from which an organism is isolated can seldom be incriminated as the 'causative focus' except in quite exceptional circumstances. Although much weight may be given to the presence of a pathogen selective positive germ in, say, a tonsil or a cervix, in no case must its presence alone be taken as a peremptory call to extirpate that focus."

2. Agglutination tests. Agglutinins to any one of four strains of hemolytic streptococci were found in only 53 per cent of tests done on 49 patients by Short, Dienes and Bauer (in 47 per cent of those less than one year old;

in 55 per cent of others). Only 24 to 36 per cent of the patients of Neil and Hartung possessed agglutinins in significant titer (1:160 and more) to certain strains (NY 5, AB 13) but not to other strains of hemolytic or to green-producing streptococci. Early work indicated that serums of most patients with atrophic arthritis agglutinated group A hemolytic streptococci; later, the serums were found at times to possess "cross-agglutinins" with other streptococcal groups. Studying this phenomenon, Wainwright noted agglutination not only of group A, but also of three strains of group B (Lancefield) streptococci. Group specificity rather than strain specificity was apparent for both groups A and B. The phenomenon is probably due to the development of multiple agglutinins for hemolytic streptococci in such cases, rather than to any crossing of the reactions between the two groups. This "does not bar the conclusion that the agglutinins present in these sera are the result of rheumatoid arthritis, and are indeed quite characteristic of the disease, but the true nature of the reaction requires further study." Others<sup>179, 617</sup> pointed out that these tests are technically difficult, impractical as routine procedures, and subject to great error in interpretation. The reaction seems highly characteristic for atrophic arthritis and may represent a specific diagnostic test indicating hemolytic streptococci are primarily or secondarily involved in the disease; however, it may be nonspecific, or rather "specific" for the disease but without etiologic significance (like the Weil-Felix or Wassermann reactions).

3. Precipitin tests. In their cases, Neil and Hartung noted precipitins for hemolytic streptococci in titers comparable to those for agglutinins. They considered precipitin tests superior to agglutination tests. But the former are of no value as routine tests (Dawson). Already noted (under "rheumatic fever") was the work of Chasis and McEwan on cross precipitation reactions in serums of patients with rheumatic fever, scarlet fever, and atrophic arthritis.

4. Antifibrinolysins. These are usually normal but may be increased in early and acute cases. Studies thereon suggest that the disease is sometimes initiated, but not kept up, by hemolytic streptococci (Dawson). Waaler noted increased antifibrinolysis in 50 per cent of 24 cases; the reaction changed with the activity of the disease.

5. Skin tests. Although the skin of patients with atrophic arthritis (also rheumatic fever) is likely to be particularly sensitive to hemolytic streptococci, Traut and Dawson considered skin tests of no value. Post, however, regarded the local and focal reactions due to intracutaneous injections of bacterial filtrates of some significance.

6. Complement. Amounts of complement were normal in 13 cases of variable severity (Rachmilowitz and Silberstein). The test is valueless in arthritis (Dawson).

7. Interpretation of immunologic data. Since progress has not been made in this matter, current comments were few and brief. There is no immunologic evidence that the disease is due to green-producing or indif-

ferent streptococci. Such evidence as there is seems to incriminate hemolytic streptococci but is incomplete, and one cannot conclude that streptococci cause the disease. Perhaps they are the sensitizing (predisposing) agent and some other factor is the direct exciting cause.<sup>39, 86, 179</sup>

*Theory of Bacterial Allergy.* The sound and the fury thereon have abated, at least temporarily, and nothing new of significance was reported. At present "allergy [as a cause of chronic arthritis] is little more than a hypothesis and a rather unsatisfactory one at that" (Dawson).

*Virus Theory.* Particles resembling virus bodies were found by Eagles, Evans, Fisher and Keith in material from patients with atrophic arthritis as well as from those with rheumatic fever and chorea. Serums from patients suffering from these diseases agglutinated the suspensions representing the corresponding diseases. Therefore, the particles seemed of etiologic significance even though their infectivity has not been proved.

*Factor of Trauma.* The rôle of poor posture as a predisposing, localizing and aggravating factor in arthritis was discussed by Hartung.

*Factor of Circulatory Disturbance.* The most diversified arrangement of nail bed capillaries was noted by Kersley in examination of normal persons and of patients with atrophic, hypertrophic and gouty arthritis. No abnormality was characteristic of any group. Atrophic arthritis has been ascribed to various circulatory abnormalities, among them venous stasis (Bernstein, 1933), varicose veins, phlebitis (Meyer, 1935). To determine what effect, if any, venous stasis has on the production of arthritis, McMaster studied 30 cases of varicose veins of long standing, with prolonged edema of ankles and feet. Roentgenographic evidence of chronic arthritis in ankles and feet was absent in 21 (70 per cent), present in nine (30 per cent) cases but only when there was both passive congestion and ulcerous infection of the leg or near the ankle. Even so, articular changes were mild.

[All but one of the nine patients with arthritis were between 52 and 83 years old; factors of age and trauma may have been responsible for the changes. A control study of a group comparable in age and weight, but without varicosities, should have been made.—Ed.]

*Factor of Altered Metabolism.* No consistent or significant evidences of disturbed carbohydrate metabolism were noted by Kersley. According to Forbes and Neale (1935, 1936) indoluria is present in most cases of atrophic arthritis, diminishes as patients improve and disappears with recovery. This suggested that indole might be a cause of arthritis (Forbes and Neale<sup>242</sup>). Marked arthritic changes were produced within a few weeks by intra-articular injections, into animals, of indole, skatole, and indole proprionic acid in a solvent. Muscle atrophy, joint swelling, crepitus and stiffness, proliferation and erosion of cartilage and capsular thickening resulted. Control joints, injected with solvent alone, were normal. The indole ring was not responsible since tryptamine (B-indolethylamine) produced no lesions. The results warrant further study but do not prove that products of putrefaction of tryptophane are responsible for atrophic arthritis.

[As the authors pointed out, arthritic changes can be produced by intra-articular injection of a wide variety of mild or strong chemical irritants from distilled water to carbolic acid. Such studies are of interest but do not prove the cause of atrophic arthritis. In these experiments the synovial reaction was not mentioned.—Ed.]

An atonic bowel frequently has been noted in arthritis; it is also a feature of vitamin B deficiency. Steinberg noted certain symptoms (digestive disturbances, lack of vigor, weakness, anorexia) common to both conditions but joint changes do not occur in experimental or clinical vitamin B deficiency. Of 24 patients (mostly with atrophic arthritis) colons of 79 per cent were spastic; of only 4 per cent atonic. [Normal in the rest?—Ed.] The spasticity certainly cannot be blamed on vitamin B deficiency. Non-arthritis were found to consume 2.3 cupfuls of vegetables daily; arthritis almost as much—1.5 cupfuls: "One could hardly surmise that a lack of vitamin B intake was an etiologic factor in chronic arthritis."

Depletion of vitamin C reserve was noted in cases of acute rheumatism, atrophic arthritis and tuberculosis by Abbasy, Harris and Ellman. The average daily urinary excretion of vitamin C was (per 140 lb. body weight) 13 mg. in normal conditions, 8.6 mg. in atrophic arthritis, 7.6 mg. in active tuberculosis; the more rapid the sedimentation rates the less the urinary excretion of vitamin C. This represents an increased destruction of, or a demand for, vitamin C in atrophic arthritis. In infective processes there is increased consumption of vitamin C. Since the results in tuberculosis and atrophic arthritis were alike, the latter disease may also be due to infection.

Race noted in various rheumatic diseases, especially atrophic arthritis, subnormal amounts of the carotinoid pigments and of vitamins A and C. "A deficiency of vitamin B is also probable but has not yet been demonstrated." Admitting that arthritis does not resemble any known specific dietary deficiency, Pemberton nevertheless restated his belief that unbalanced nutrition may, with other factors, pave the way for the production of either type of arthritis.

*Factor of Endocrine Abnormality.* This idea found no support. There is considerable doubt whether endocrine dysfunction alone can produce atrophic arthritis (Poynton).

*Neurogenic Factors.* Psychic trauma has been cited by some as a precipitating factor, by others as perhaps the actual cause of atrophic arthritis (Jones 1909, Smith 1932, Nissen and Spencer 1936). Thomas found notable emotional disturbances antedating arthritis in all of 31 cases; in nine cases severe depression developed weeks or months before, and became less marked after, arthritis had developed. The phenomenon was unexplained.

*Conclusions on Etiology.* It is only too apparent that the year under review recorded no striking progress in the problem of causation. Writers seemed less enthusiastic about arguing their favored theses; perhaps this dissatisfaction with existing hypotheses should, of itself, be recognized as progress. Some regarded the pathologic reaction in joints (no polymorphonuclears, negative cultures) as strong evidence that the disease is not

due to intra-articular germs. In a few cases in which Fisher found streptococci in joints, the pathologic reaction in synovial membranes was typically pyogenic with intense polymorphonuclear infiltrations, representing a secondary infection; in these cases toxic foci were obvious but not in others. The majority of writers still supported the infectious theory as the most likely one but did so rather dispiritedly. Others warned against its acceptance as a bar to progress. "It is curious how easy the recognition of any organism lulls for a time at least the urge for further inquiry: Many workers having isolated a given organism from a focus, from blood or synovia are prepared to accept the findings with such absolute finality that the door of research is closed not only against other obvious causal factors but even against inquiry as to how the germ in question produces its results" (Miller).

*Relationship between Atrophic Arthritis and Other Diseases.* 1. Rheumatic fever. Some<sup>201, 237</sup> expressed the belief that the relationship between atrophic arthritis and rheumatic fever is extremely close because the articular pathology of the two seemed similar to them and because in both diseases "virus bodies" were found, cross agglutination of which occurred with regularity. "While it cannot be said that their etiology is identical, it is at least probable that they possess some common significant factor which is reflected in serological tests."<sup>201</sup> However, having studied the nodules in both conditions Collins was unable to postulate a pathologic relationship between the two diseases. Master, Jaffe and Dack reported the case of a young girl with chorea, pericarditis, mitral and aortic endocarditis and attacks of migratory arthritis who later developed the characteristic picture of chronic atrophic arthritis (deformities, ulnar deviation, etc.). [The clinical description bears out the distinction drawn.—Ed.] The likelihood of a common etiology was considered but discarded; the combination was considered probably coincidental, two distinct diseases affecting one patient.

2. Still's disease. This was discussed earlier in this review.

#### TREATMENT OF ATROPHIC ARTHRITIS

*General Remarks.* In need of correction is the attitude of those physicians who believe that arthritis is a more or less hopeless problem.<sup>126</sup> In need of sharper correction are those too numerous patients who demand quick cure. Having ignored their physician for months on end while sampling the ancestral and neighborhood "cures" this type of patient finally comes "barging" into the physician's office and sometimes acts as if the physician himself had invented the disease and was personally responsible for its prompt eradication. The physician is expected to "pull a miracle out of his sleeve" or else —. The physician is quite aware of his patient's unspoken words, "I'll give this fellow just so many weeks, after that no more nonsense." Physicians must not be offended by the tactics of such patients; they are sick, distraught human beings who are simply and unconsciously acting on the principle that the best defense is an offense.

But for them especially and for all arthritics the physician should, at an early consultation, make clear what both he and the patient are up against. A tuberculous patient accepts the necessity for prolonged, unspectacular treatment. Similarly, arthritic patients must learn the necessity of a long and perhaps tedious program of useful but undramatic measures. And at the start they must learn what their relationship to the physician is to be. Such is the nature of the disease that although as "quarterback" the physician must "call the signals" it is the patient that must "run with the ball." Unfortunately in this disease the patient cannot yet do as he would like to do—sit comfortably on the bench and applaud the physician's battle. Too infrequently can the physician by some lucky tour-de-force rapidly cure his patient but he can often teach the patient how slowly to "cure" himself. Therefore the first principle is, as Wyatt put it, for the physician to "put all the cards on the table" and unless the patient is prepared to "play the game through to the end" it is far better (for the physician) not to start at all.

In the absence of precise knowledge of etiology, most treatment is symptomatic or empirical but many of the finest treatments in medicine have been based on empiricism.<sup>740</sup> In advancing the cause of the arthritic it is far better for physicians to understand and apply the standard procedures of known value than to accept too hastily the new "cures." The following, written by Pelouze<sup>537</sup> in another connection, is applicable to the field of rheumatism: "In these restless days when every new, near-new or old thing in the way of treatment of disease is scrutinized by our commercial brethren for its dollar making possibilities, it behooves us to place ourselves in a position in which we are not swayed foolishly into heights of enthusiasm that offer our patients but little. Far too often we have been the stepping stones over which the commercially inclined have travelled to their dollar harvests." As McCarty wrote "The only new panaceas and specifics in this condition are quite old: Careful study and long hard work."

*Management of Foci.* In the literature under review the optimists regarding removal of foci were a shade more numerous than the pessimists. Wrote the latter: It is all too obvious that removal of infected foci does not necessarily cure arthritis<sup>455</sup>; only in a minority of cases can infected foci be found and the results of their removal are mostly disappointing.<sup>740</sup> Wrote the former: There has been too much talk and too little action about removing foci. If foci are removed within six months of the onset of arthritis the patient usually recovers without further treatment.<sup>126</sup> Hamilton advised "radicalism within the limits of common sense" and Haden concluded that focal infection is only an influencing factor, not the one of chief importance. Nevertheless, it is unwise to allow evident focal infections to remain. They should be removed in mild cases early; in more advanced cases when patients are "on the up-grade." Buckley expressed the belief that following removal of foci a sufficient number of complete recoveries have been noted to indicate that such foci may be of etiologic importance.



Removal of foci was never unwise in principle but has been expected to accomplish the impossible.

Wholesale removal of teeth was condemned; no tooth should be removed until a roentgenogram of it has been made. Infected teeth should be removed, also pulpless or partially erupted teeth, if a more definite focus has not been found. Alveolectomy is not a panacea but may be of definite nonspecific value (Dunn). Scott regarded alveolectomy as too often a "ritual" which the "wise men" feel they must observe. Breuning described the local indications for tonsillectomy and considered age per se no contraindication to tonsillectomy. Regardless of age, death had not occurred in the course of 1800 tonsillectomies and Breuning cited the experience of Turnley who had observed 76,000 tonsillectomies without a hemorrhagic death. Electrocoagulation was not advised. In the presence of atrophic arthritis, according to Cohen, "Whenever tonsils are diseased they should be removed; in fact (considering our inability to pre-judge tonsillar infection) whenever tonsils are present they should be removed." According to Hurd, "silent sinusitis" (no headaches or frank pus) is frequently an important focus, eradication of which may relieve joints. When the gall-bladder of an arthritic is presumably diseased, the indications for cholecystectomy must be determined on the basis of the gall-bladder and not of the joints. Taylor expressed the belief that genito-urinary foci were sometimes the sole cause of arthritis. Barrows noted the various surgical and nonsurgical methods of treating pelvic foci. The surgical correction of toxic absorption from cecal stasis was approved by Schmoele.

[Lane's idea (1924) found its firmest American foothold in California; it has been largely abandoned elsewhere. It is difficult to incriminate cecal stasis when atrophic arthritis has, as far as we know, never been reported as a sequel to Hirschsprung's disease. In general, operations for the correction of cecal stasis have had only a transient beneficial effect on arthritics, similar to that of any (incidental) surgical procedure involving anesthesia, rest in bed, postoperative fever, altered diet, convalescence.—Ed.]

[In closing this discussion may we paraphrase some remarks on fever of unknown origin, by Hamman and Wainwright, remarks most applicable to arthritis: The impression has strongly prevailed that [arthritis] is commonly due to hidden foci of infection. This conception has dominated medical practice during the last 25 years. Never before in modern times has a theory of disease so completely captured the imagination of the profession and been so enthusiastically followed in practice. The theory is extraordinarily beguiling, because it explains simply and directly many of the most abstruse and bewildering problems in pathogenesis and still more so because it offers an equally simple and direct rule of practice. No patient can feel neglected while his body is being scrutinized thoroughly and the searching tests of science applied with meticulous care to every function. Nor need any physician be oppressed by the sense of fruitless inactivity so long as there are teeth to be pulled, tonsils to be enucleated, sinuses to be reamed, thyroids to be excised, gallbladders to be drained, appendices to be removed and kidneys to be probed. For a while the practice of medicine became almost solely a routine search for foci of infection and the practice of surgery a routine removal of foci. Science was rampant. . . . Those were the glorious and profitable years, cut short, alas by the onset of the financial depression!]

*Vaccines, Antigens, Filtrates.* Crowe was convinced that of any single method of treatment vaccines give "far and away the best results." Of 5000 patients given his mixed vaccine, 85 per cent received some benefit (details not given). However, he admitted that other forms of therapy also should be used. Ishmael and McBride "desensitized" 100 patients with vaccines from several strains of arthrotropic streptococci: "88 became pain free and sedimentation rates returned to normal in two months' therapy." Of Banister's 20 patients 19 were "greatly benefited" from intravenous injections of a vaccine made of hemolytic streptococci recovered from the blood in one case by the method of Gray and Gowan (1931). Thompson and Wyatt considered vaccines highly beneficial in a large percentage of cases in which sedimentation rates were high and agglutination titers were low. Vaccines have a definite place as part of a therapeutic program but not as a specific, according to Overholt and Mortensen, who considered stock vaccines of arthrotropic streptococci (e.g. Lederle's *Streptococcus hemolyticus* vaccine) preferable to autogenous strains of unknown tropism. Vaccines were given intravenously in small doses for four to 12 months. Haden saw no objection to them if used as nonspecific adjuvants. Post treated 175 patients with an "autogenous streptococcal toxin" (filtrate); 83 per cent were improved.

Most of these reports are subject to the criticism of Jordan: No satisfactory control of vaccines from the standpoint of laboratory tests and pathologic modification has been reported. Most workers fail to report any controls and treat patients so long that natural remissions have time to occur. It may be justifiable to use vaccines in selected cases under close observation but not with the implication of specificity or of certain cure; the use of vaccines in arthritis rests on pure empiricism. Vaccine therapy was considered unreasonable by Okell who found it impossible to believe that streptococci cause atrophic arthritis when they are practically never found in joints or lymph nodes, even in acute stages of the disease. Green streptococci will produce arthritis of animals (experimentally affected) and (rarely) of man but in both cases the arthritis is purulent and bears no resemblance to atrophic arthritis. There is no evidence convincing to Okell that vaccines ever cured any human disease of known bacterial causation. Yet we are asked to believe that by injecting dead bacteria, a method apparently without curative value in any human or animal disease, we can benefit a disease of unknown etiology which may not be microbic at all. The effects of vaccine can be studied only by scientific statistical methods, without the use of which no physician should take it on himself to express an opinion of vaccine or any other therapeutic measure in a disease as subject to fluctuations as is this.

Having achieved no results from intravenous injection of vaccines, Cohen regarded more highly the "antigen treatment" with filtrates of *Streptococcus cardio-arthritidis*. Desensitizing doses were given subcutaneously. Many patients recovered completely (no details given). On similar

principles Gordon<sup>202</sup> used filtrates (autogenous or stock) of streptococci to which patients were skin sensitive, filtrates being detoxified by formalin. Of 100 patients so treated, improvement was marked in 43 per cent, moderate in 26 per cent, slight in 16 per cent, absent in 15 per cent.

[As we have noted previously, streptococcal skin tests are notoriously unreliable. Others have regarded them unsuitable as indexes for selection of vaccine.—Ed.]

*Foreign Proteins.* These may be of value in chronic cases but may be harmful in seriously acute cases.<sup>151, 282</sup>

*Chaulmoogra Oil.* The idea behind this therapy was the observation of McIlhenny (1926) that leprosy patients treated with chaulmoogra oil seemed exempt from arthritis. Beneficial results from intramuscular injections of the oil into arthritic patients were reported by McIlhenny (1931) and Hebert (1933). Robinson treated 225 patients with arthritis of various types, mostly of the "infectious" (including gonorrheal) and atrophic types. If deformity was not marked the chaulmoogra oil was "very efficacious" (detailed results not given). Focal and general reactions (malaise, slight fever) were produced by the injections. The oil was injected intramuscularly; abscesses, usually sterile, were produced in 11 cases in which unabsorbed oil accumulated between fascial layers.

[It would appear that the reactions were analogous to those from injections of mild foreign protein and the results no better. The latter treatment would seem preferable to one which produced abscesses, even though only in 5 per cent of cases. We would agree with a recent comment concerning this therapy: "It seems suggestive that although seven and five years have elapsed since the publication of their 'preliminary results' neither McIlhenny nor Hebert has seen fit to report further."—Ed.]

*Bee Venom.* Patients frequently inquire about this; no reports thereon appeared in 1937.

*Diets.* The rationale of his dietary program was reviewed in detail by Pemberton, who advised the following: Calories—to meet the individual energy requirements; proteins—about 1 gm. of protein per kg. of body weight, or about 15 per cent of the calories needed; carbohydrates—to supply 33 to 50 per cent of calories needed; fats—to supply 50 to 33 per cent of calories; abundant minerals, vitamins. The diet should not become a "routine" and should be only one factor in treatment. To reduce the intake below the minimal maintenance level is not often indicated and then only for brief periods. A reduced diet should not be given to febrile patients or to those fatigued or at work. Haden approved a diet low in carbohydrates, with adequate vitamins and vitamin supplements (wheat germ, yeast, vagex) and abundant proteins. Cnunt noted no beneficial results from the use of a low carbohydrate diet in cases of "chronic rheumatism" and "deforming arthritis" (no details given).

Others insisted that there is no such thing as a specific diet for such patients (Haden, Wyatt) and no need to avoid meats or citrus fruits (Copeman and Tegner). "Anything that will agree with the patient should be permitted freely" (Cohen).

*Additional Intestinal Therapy.* High colonic irrigations still found support.<sup>126</sup> Pemberton warned against the excessive use of purges or of bran in amounts which may form mechanical irritants. To correct constipation, Phillips' patients were occasionally given magnesium sulfate and nothing but orange juice for 24 hours.

*Vitamins.* In atrophic arthritis there may be a deficiency of certain vitamins; the serum may be low in vitamins A and C; a deficiency of vitamin B is also probable, according to Race, but has not yet been demonstrated. These deficiencies are common to various rheumatic diseases, are not specific or striking, and their significance is not clear. Vitamin A was prescribed by some (Ishmael and McBride). Vitamin B contains two better known factors ( $B_1$  and  $B_2$ ), perhaps six others. Some of the symptoms of  $B_1$  avitaminosis (polyneuritis, lymphopenia, excess lactic acid) are absent in atrophic arthritis; others are sometimes present (e.g. reduced glucose tolerance, subnormal temperature, muscle atrophy); but atrophic arthritis obviously is not a  $B_1$  avitaminosis (Race; Steinberg). Some, however, recommended vitamins  $B_1$  and  $B_2$  as adjunct therapy.<sup>342, 657</sup> Some believed the use of vitamin C helpful.<sup>342</sup> The results ascribed to raw vegetable diets are probably from its vitamin C content, according to Abbasy, Harris and Ellmann, rather than from its low sodium chloride content (Hare, 1936). Race adjudged the results of vitamin C therapy so far "abortive."

The working hypothesis behind Reed's (1935) use of massive doses of vitamin D in arthritis is that there may be an obscure disturbance in calcium metabolism which vitamin D somehow "stabilizes." This therapy was not "specific" however. Reed studied the total calcium exchange in arthritics under such treatment: There was no consistency in the changes of blood and urine calcium and phosphorus, in relation to effects of therapy, except that urinary calcium always increased when improvement occurred but the increase later ceased; thereafter bone density increased, suggesting that the decalcified arthritic bones were recalcified. Steck regarded this therapy nonspecific, unrelated to any definite deficiency of vitamin D in arthritis but "a most beneficial adjunct." He studied the mineral metabolism in "arthritis," considering it of no significance to separate atrophic and hypertrophic types. In most of his cases there was a disturbance of calcium metabolism, not evident in blood but evident as an altered balance, sometimes positive, sometimes "irregularly negative" (details not yet reported). Under vitamin D therapy calcium increases, first in blood, then in urine; then blood calcium becomes normal. When urine calcium increases, improvement begins. An even calcium balance ensues; later urinary calcium decreases and a positive balance is established, associated with recalcification of bones and progressive clinical improvement. But other treatment was then added as "physiologic equilibrium cannot be obtained through the mediation of vitamin D alone." From 150,000 to 300,000 units daily were given. Toxic symptoms (nausea, frequent uri-

nation, lassitude, anorexia, polydipsia; in more severe cases vomiting, gastrointestinal pain, diarrhea) occasionally appeared but ceased if administration of the drug was stopped, or was combated by brewers' yeast. Of an unstated number of patients, 75 to 80 per cent were "benefited."

[We are reminded that at a meeting where one speaker after another was reporting improvement of 75 to 80 per cent of arthritic patients treated by diverse methods, the late Dr. Joseph Miller was overheard to say "There it is again—the inevitable 75 per cent!"—Ed.]

The effect of massive doses of vitamin D on 64 dogs and 773 human beings was studied by Steck, Deutsch, Reed and Struck. Human beings and dogs generally tolerated 20,000 units per kg. per day indefinitely without toxicity. Hypervitaminosis D produced cell injury first; then deposits of calcium. The process was reversible and reparable if administration of the drug was stopped promptly. Intoxication for short periods did not produce demonstrable permanent injury.

Farley gave ertron to 27 arthritics of either type; usually 200,000 to 300,000 units, in stubborn cases 600,000 units, in one case 1,000,000 units, daily, for unstated periods. Toxicity was seldom seen with doses less than 400,000 units daily. [Some of us have noted toxic reactions to such doses.—Ed.] "In severe cases of atrophic arthritis reduction or disappearance of pain was observed. The x-rays have shown remarkable reparative changes in the joints consisting of filling in of the rarefied regions and reconstruction of cartilage: In severe cases of hypertrophic arthritis, granular resorption of exostoses, particularly on vertebrae, and reconstruction of cartilage takes place. Not a single one of this group has failed to respond in some degree to the high vitamin D therapy." Blood calcium and phosphorus remained normal in all but two cases; sedimentation rates dropped. However, high vitamin diets were used, and in severe cases hyperpyrexia also.

[In view of our own experiences and that of others, including those who originated this therapy, it is difficult to understand how vitamin D can have two diametrically opposed actions and fill in rarefied areas of bone in one region and resorb bony exostoses in another. How can it restore damaged cartilage in atrophic and hypertrophic arthritis? Pathologic evidence was not offered and the author's interpretation of his published roentgenograms seems erroneous to us.—Ed.]

Others condemned the use of massive doses of vitamin D as dangerous and as being without a theoretical or practical basis.<sup>126, 342</sup> Some, who considered the treatment "overdone," noted "disastrous results" in acute cases and increased pain and heat even in chronic cases in which 100,000 units were given daily (Ishmael and McBride). However, the usual small doses were recommended as tonics.

There are several preparations of concentrated vitamin D, including viosterol, calciferol, drisdol, Con-Dol and ertron. The use of all of these preparations for arthritis was inferentially frowned on by the Council of Pharmacy and Chemistry<sup>158</sup> which would not accept Con-Dol and Ertron for "New and Non-Official Remedies." On investigation the Council

found no definite evidence that the doses used were nontoxic or effective. They found no scientific evidence to support the claims made and deprecated the unwarranted exploitation of these products by certain manufacturers. [The report of Abrams and Bauer, just published, concludes that the use of massive doses of vitamin D in atrophic arthritis is of "little or no value."—Ed.]

*Miscellaneous Medicines and Other Substances.* Laymen are likely to think that no cure can be complete without its bottle.<sup>661</sup> However, in atrophic arthritis medicines are of little value. As one writer<sup>29</sup> put it: "Of the hundreds of heralded cures and reliefs with which the pharmaceutical houses flood the literature and our offices I have yet to see one live up to its promises." Nevertheless the arthritic, with his broken morale, can gain new confidence from the judicious use of simple analgesics.<sup>342, 374</sup> The continued use of certain drugs listed by Archer and Discombe may be toxic to some persons. Certain drugs may promote the formation of compounds with hemoglobin, decreasing its oxygen-carrying power: These include the aniline derivatives, such as phenacetin, acetanilid and certain acetylsalicylic acid compounds. Sulfonal, trional and tetranol occasionally produce sulfhemoglobin. Some drugs may cause the disappearance of granular cells of the blood: e.g., pyramidon, allonal, cibalgine, novalgin. The occasional toxicity of phenylcinchoninic acid derivatives is well known. Few patients are susceptible to salicylates or acetylsalicylic acid (aspirin). The perfect form of aspirin, according to one writer,<sup>169</sup> was a stabilized calcium aspirin. The relative merits of aspirin, calcium gluconate-aspirin and calcium phosphate-aspirin were evaluated by Serby and Sideman. For 46 patients with various types of arthritis (six atrophic, 35 hypertrophic, five others) all three drugs were equally analgesic but calcium gluconate-aspirin seemed to produce fewer and milder symptoms in gastrointestinal and circulatory systems.

The "most valuable" of all drugs to Haden was arsenic, used routinely in the form of neoarsphenamine. The intravenous use of ammonium ortho-iodoxybenzoate (Young and Youmans, 1926) fell into disrepute because of occasional serious toxicity; oral compounds presumably were helpful (Smith 1927, Cottrell 1927). Cohen considered the small doses used by others of little value and recommended calcium ortho-iodoxybenzoate (oxoate B), 1.5 to 6 gm. daily; av. 3 gm. The higher doses, although not tolerated by 24 per cent of 125 patients with atrophic arthritis, were more effective: 4 per cent were "cured"; 33 per cent, much improved; 17 per cent, improved; 22 per cent, unimproved.

[Benzoates of one sort or another frequently have been hailed, later abandoned, for arthritis. The newest one is "arthranol," recently given wide publicity in a lay magazine but condemned in the *Journal of the American Medical Association*.<sup>206</sup>—Ed.]

A bizarre and daring procedure was described by Wilms. Having thereby treated malignant syphilis one thousand times without a death, he agreed to give it to a woman aged 65 with "chronic rheumatism" who re-

quested it. For two years the patient had had swollen knees and ankles; painful hips, spine and elbows, and anterior crural and sciatic "neuritis." Treatment consisted of giving "lethal doses of mercuric chloride per os antidoted in five hours with calcium sulphid intravenously grain for grain of the mercuric chloride." A protocol of the patient's immediate reactions is given. Treatment was begun at 11 a.m.: "All pain had left her about 2:00 p.m." It was stated that the procedure could be repeated if necessary several times, with several weeks between treatments. With candor Wilms wrote, "The theory of action of the procedure had better be let alone for the present; there are a few things to think about."

[Especially do we agree to the last part of his quotation. This is apparently the first patient with arthritis he has so treated. No statement as to the patient's condition after the second day was given. Data given are inadequate for one to determine what type of chronic rheumatism she had. In the hands of anyone not familiar with this procedure death might well result.—Ed.]

[Every few months some new drug is exploited for arthritis so assiduously either by unfortunate newspaper publicity or by zealous commercial interests that most physicians at once become suspicious of them regardless of their merit or lack of merit. But arthritic patients soon hear of such drugs and pester their physicians for advice and information thereon. The latter is often difficult to find since the drugs are rarely recommended in the more widely read journals. We shall, therefore, occasionally refer to certain articles in obscure journals so that physicians who wish may read them, we hope with a properly critical attitude.—Ed.]

Causalin (amino-dimethyl-pyrazolon-quinoline-sulphonate) was used for "rheumatism" by Latzel (1927, 1928) in Germany. Two current American reports are noted. One writer<sup>631</sup> treated an unstated number of patients with atrophic and hypertrophic arthritis "which are related conditions, not distinctive diseases," and concluded, "after a four months' study," that results were "promising." Brief abstracts of four cases were given but no other details. Another physician<sup>585</sup> combined causalin with washing of the bowel and hyperpyrexia: 62 patients were treated, exemplifying atrophic, hypertrophic and gonorrheal arthritis, synovitis, fibrositis, and sciatica, even one patient with "secondary hypertrophic osteo-arthropathy" with pulmonary moniliasis (from data given we cannot accept the last diagnosis). Results were "remarkable improvement" in 84 per cent, partial improvement in 11 per cent, none in 5 per cent. Causalin is just another name for causyth. In 1930 the Council on Pharmacy and Chemistry of the American Medical Association condemned causyth as "therapeutically worthless and ineffective except for possible shock effects which might be dangerous." Causalin has likewise been condemned by the Council<sup>159</sup> as a mixture without originality or rationality, "an unsafe and dangerous product" (among other things it contains aminopyrine).

Last year "subenon" was first brought to the attention of the profession via the lay press and was quickly investigated (and condemned) by the Bureau of Investigation of the American Medical Association.<sup>172, 203</sup> "Subenon" (Seydel Chem. Co.) is the calcium double salt of benzoic and

benzyl succinic acid. Over a period of two years 200 patients with atrophic and hypertrophic arthritis were treated.<sup>410</sup> With the idea that arthritis is related to intestinal derangements the drug was used (in 60 cases with other remedies) as an intestinal detoxifier. Results were excellent in 5 per cent, good in 27 per cent, moderate in 30 per cent, slight or absent in 38 per cent. "No mention of control cases has been made. It is my opinion in the face of unlimited references that all cases treated in other ways could be considered control cases, and I did not deem it necessary to repeat such clinical experiences."<sup>410</sup> [The American Medical Association<sup>172, 208</sup> has again called claims made for subenon "ridiculously optimistic."—Ed.]

*Sulfur.* Since his previous reports on 250 patients with "arthritis" Woldenberg has treated 106 more. In 82 per cent of these 356 cases (types not definitely stated) patients were "free from pain after the sixth injection." Colloidal "sulphur-diasporal" was given intravenously rather than intragluteally as before. "Arthritis" was considered "a metabolic disorder superimposed by infection."

Having observed most of Wheeldon's cases (1935), Clark stated that best results were obtained by giving, in cases of "hypertrophic and mixed arthritis," colloidal sulfur (sulicosol) intravenously in large doses (*total* dosage 360 to 1060 mg., av. 600 mg.; average weekly dose 126 mg.). Of Clark's own 20 patients (representing hypertrophic and mixed types) seven were subjectively, all were objectively, improved. In six years Wheeldon treated with sulfur more than 1500 patients with "arthritis." He developed a "new sulfur preparation," given intravenously, supplemented by the oral use of an "adrenal cortex" (both preparations undescribed). The adrenal cortex presumably improved the patients' sulfur reserves when given alone but even more when used with colloidal sulfur (no data given). Results were not analyzed statistically but were "romantic."

After four years' work with colloidal sulfur Hamilton seemed to damn it with faint praise; the best he could say for it was that he was "favorably impressed." Parmenter gave sulfur baths and sulfur orally to 47 patients with atrophic arthritis: Results were "satisfactory" in 64 per cent of cases; relief was incomplete in 28 per cent, absent in 8 per cent.

[Many of us have used various sulfur preparations, colloidal and otherwise, and have abandoned them as worthless. It would seem easy to confirm statements that 80 per cent or so patients can be promptly freed of pain. We simply cannot confirm this and note few converts to this therapy. Practically all who write on it neglect even to diagnose the types of "arthritis" treated, to study controls or to be critically scientific. Just recently the Council on Pharmacy and Chemistry<sup>160</sup> made a detailed and very unfavorable report on the use of colloidal sulfur for arthritis.—Ed.]

*Gold.* The curve of acceptance of most "new" treatments for arthritis that are destined to be discarded, rises rather rapidly, reaches its peak in about three to five years, then falls as adverse reports begin to outnumber the optimistic ones. Finally, use of the treatment in any significant degree dies out after about 8 to 10 years. As one physician advised, "make haste



to use a new remedy before it is too late." <sup>714</sup> Unfortunately they are, like the cat, possessed of nine lives and usually linger on too, too indefinitely, as some laggard "researcher" thinks he has discovered their supposed merits and keeps them going, with the help of the commercial houses. American physicians, aware of the supposed value of gold for arthritis but concerned about its toxicity, have been slow to use it, expecting it would die out or be made safer. It therefore seems significant that the curve of acceptance of chrysotherapy is still rising after 10 years of use. At the recent International Conferences at Oxford and Bath gold was the subject of many informal conversations. Two of us (F. C. H. and P. S. H.) were impressed by the restrained yet sustained enthusiasm for this therapy expressed by numerous British and continental physicians of long experience and unquestioned ability, and in England not only by rheumatologists but also by professors of medicine not primarily interested in rheumatism. Current reports on chrysotherapy for arthritis continue to call it, "the medicament of choice in early cases" (Copeman and Tegner), "very impressive though far from miraculous" (Parr and Shipton), "the best means of combatting the disease" (Sashin and Spanbock), "of undoubted value, the best single form of treatment" (Hartfall, Garland and Goldie).

[In view of this, but without meaning to lend our personal approval to it as yet, we shall again review current reports in some detail. Most of us have not used it extensively. The preliminary American report of Snyder, Lust, Traeger and Kelly may be consulted and that of one of us, A. J. K., will shortly appear. In the meantime the report of Hartfall, Garland and Goldie should be "required reading" for those who plan to use this treatment.—Ed.]

Some of the gold compounds used were:

- Allochrysin—auro-thio-propanol sulphonate of sodium
- Crisalbine—gold sodium thiosulfate
- Lopion—auro-allyl-thio-urea benzoate of sodium
- Myochrysin (myocrisin)—auro-thio-malate of sodium
- Sanocrysin—double thiosulfate of gold and sodium
- Solganol B—auro-thio glucose
- Triphal—sodium auro-thio-benzimidazole carboxylic acid

Five reports appeared (two British, one Irish, one Australian, one American) all attesting to the value of chrysotherapy for atrophic arthritis. The least significant report was that of Crawford who gave other forms of treatment with the gold [type of gold used not stated definitely.—Ed.] Of 13 patients three (23 per cent) were "cured," five (38 per cent) very much improved, four (31 per cent) improved, one (8 per cent) relapsed. Sashin and Spanbock treated 22 patients: 12 (54 per cent) were markedly improved, five (23 per cent) slightly improved and five (23 per cent) unimproved. Six months later two patients had had slight relapses, promptly relieved by another course of gold sodium thiosulfate. Copeman and Tegner treated 51 patients (46 with atrophic arthritis, three with ankylosing spondy-

litis, two with "peri-arthritis") with allochrysin. There was "great improvement or cure" in 58 per cent, improvement in 36 per cent, no improvement in the three cases of spondylitis (6 per cent). The majority received one course; several, two courses. Parr and Shipton treated 70 patients with atrophic arthritis by means of myocrisin: 7 per cent were cured, 50 per cent greatly improved, 13 per cent slightly improved, 10 per cent unchanged, 10 per cent worse; 3 per cent had recurrence; 6 per cent stopped treatment because of reactions, and one patient (1 per cent) died in a toxic reaction.

Following up their series of 1935, Hartfall, Garland and Goldie have made an excellent report of the good and bad results noted in the treatment of 900 patients with arthritis (750 of atrophic type). Their report is so detailed and comprehensive that we cannot here review it completely; all interested in gold therapy should read it. Of the 750 patients with atrophic arthritis treated, 690 completed the treatment. Of these, 10 per cent were cured, 57 per cent markedly improved, 13 per cent moderately improved, 6 per cent slightly improved, 9 per cent unchanged, 2 per cent worse, 3 per cent dead. Follow-up was made in 300 cases. Crisalbine and lopion were given intravenously, solganol B oleosum and myocrisin were given intramuscularly. A careful analysis of relative effectiveness (and toxicity) of each compound revealed that the same number of patients "improved" with each drug, but there were more "cures," and also more toxic reactions, from crisalbine. Preparations given intramuscularly were as toxic as those given intravenously but the former route was easier.

In general, results were better among those who had more than one course and, as one might expect, among those whose arthritis was of shorter duration. Sedimentation rates usually fell during treatment but changes in rate were not always related to results. Some patients improved definitely although their rates fell only slightly or even rose.<sup>296, 521</sup> Of the cases of Copeman and Tegner, rates fell in 69 per cent, continued to rise in 4 per cent, were unchanged in 18 per cent. In 9 per cent the rates rose before they fell; a rising rate after treatment is begun is therefore no prognosis of failure. However, in this series no patient improved whose rate persistently failed to drop. In the cases of Sashin and Spanbock the effect of chrysotherapy on sedimentation rates was notable. Sedimentation rates in the entire group of 22 cases totalled, before treatment, 1051 (av. 48) mm., after treatment, 604 (av. 27) mm. The drop was most evident in 12 patients markedly improved: total rates before treatment, 558 (av. 47) mm., after treatment, 126 (av. 11) mm. Rates of the 10 patients not significantly helped were, total before treatment, 493 (av. 49) mm., after treatment, 478 (av. 48) mm., all rates being after 45 minutes of sedimentation.

Contraindications to chrysotherapy were few: gross renal or hepatic disease, colitis, pregnancy, eczema, severe anemia, a history of previous purpura or agranulocytosis. On the basis of their experiences with toxic reactions Parr and Shipton considered it dangerous to treat arthritic patients with pronounced malnutrition, sweating, cyanosis, tachycardia (the cold, clammy, cyanotic young woman), until

improvement had been effected otherwise; also, to treat patients with edema of feet and ankles.

Plans of dosage varied somewhat but there has been a progressive tendency to use smaller individual and total doses, with several weeks' intermission between courses. Results did not seem entirely dependent on the total amounts given. Copeman and Tegner gave allochrysin intramuscularly every four to seven days: initial dose, 10 mg.; second dose, 20 to 50 mg.; highest individual dose, 100 mg.; total dose for one course, 1 to 1.5 gm. Having had toxic reactions from larger, ascending doses of myocrisin, Parr and Shipton reverted to an initial dose of 10 mg., later doses each 50 mg., no higher, given once a week for 12 doses. Crawford gave 10 mg. of gold at the first dose and again four days later, then every four or five days (schedule—10, 10, 20, 20, 50, 50, 100, 100, 200 and 200 mg.; thereafter every five to seven days 200 mg.; no higher dose). Sashin and Spanbock gave equal doses (5 c.c. gold sodium thiosulphate) once or twice a week intravenously for 25 to 40 injections; if relief was not noted from 25 doses, use of the drug was stopped. Having originally given larger single doses and a total dose of 2 gm. each course, Hartfall, Garland and Goldie strongly urged reduction in individual and total doses: maximal individual dose, 100 mg.; maximal total dose for one course, 1 gm.; injections to be given weekly for about 12 weeks (first dose, 25 mg.; if no pain, second dose 50 mg.; third and subsequent doses, 100 mg. each).

"Every patient should have at least two courses"; this was the opinion of most. Relapses often occur after the first course; less often after two courses. Patients rarely have more than one relapse. With differing plans of dosage the interval between courses varied: four weeks (Parr and Shipton); six to eight weeks (Copeman and Tegner); no less than three months because toxic reactions from the first course may not appear until six weeks after stopping of the treatment (Hartfall, Garland and Goldie; Parr and Shipton). If then the sedimentation rate is still elevated another course should be given.

Toxic reactions were unfortunately frequent though their danger is overestimated according to Copeman and Tegner. Reactions noted by some were not serious: They occurred in 12 (44 per cent) of Crawford's 27 cases: albuminuria in seven, pruritus in nine, rashes in seven, diarrhea in one, stomatitis and "metallic taste" twice each; more than one reaction sometimes occurring in one person. Of the 22 cases of Sashin and Spanbock reactions occurred in four (18 per cent): stomatitis twice, pruritus and urticaria once, pruritus once. Copeman and Tegner noted toxicity in 10 of their 51 cases; reactions were severe in only three cases, and treatment was stopped in only three cases. Reactions were mild: transient dermatitis in two; severe exfoliative dermatitis lasting three months each in two; diarrhea in three; malaise in two; stomatitis and pruritus once; mild albuminuria alone was not considered a cause for stopping treatment. Parr and Shipton noted reactions in 18 (26 per cent) of 70 cases: in 16 of 48 females, but in only two of 22 males; females therefore seemed four times as sensitive as males. There was no relation between age and toxicity. Noted were dermatitis in 10 cases (exfoliative dermatitis in two), affections of mucosae in four, and hemorrhages (uterus, lung, bowel) in five cases. [Since this adds to 19 reactions it is assumed one patient had two types of reaction.—Ed.] The hemorrhages were all among women; one was almost fatal and one was fatal. A young woman died from uncontrollable uterine hemorrhage after receiving 200 mg. as the second dose of her second course, a dose apparently too high for her.

The most comprehensive analysis of toxic reactions, given by Hartfall, Garland and Goldie, deserves close reading. Of their 900 patients treated, trivial reactions occurred in 7 per cent, more significant reactions in 35 per cent, reactions of any kind in 377 cases or 42 per cent. Reactions were slight in 145 (16 per cent), moderate in 178 (20 per cent), severe in 54 (6 per cent) cases. Among the 900 patients, 262 had skin reactions (mostly mild but severe in 28, including five cases of ex-

foliative dermatitis); 75 had stomatitis; 50 had mild enteritis; 85 had jaundice; nine had purpura, one each had agranulocytosis, hypochromic anemia and macrocytic anemia. [Apparently some patients gave multiple signs of toxicity as this totals to 484 reactions in presumably 377 cases.—Ed.] Toxic reactions were more frequent in the first course, less frequent thereafter, but some escaped reactions in the first course, to get them in later courses. When toxicity was apparent, administration of the drug was stopped for two months but a common toxic reaction was not considered a contraindication to further treatment later. According to some,<sup>521</sup> in the order of decreasing toxicity were triphal, sanocrysin, solganol and lopion. Preparations used by Hartfall, Garland and Goldie were equally productive of severe toxicity but crisalbine produced more of the less severe reactions (and more cures). The gold content of any preparation was not the chief factor in determining toxicity; chemical composition seemed more important.

Jaundice, presumably of the catarrhal type, from toxic hepatitis, affected 85 patients; it was slight in 22, moderate in 50, severe in 13 (fatal in two). Curiously, jaundice did not develop in any of the first 100 cases of these workers. The condition, when it occurred, may have arisen in part from an epidemic of "infective hepatic jaundice" which occurred in the region. No ameliorating effect from jaundice was noted in any case.

[Serum bilirubin values were not noted. A certain intensity (serum bilirubin about 8 to 10 mg. or more per 100 c.c.) is apparently necessary before the ameliorating effect of the common types of jaundice is noted, as one of us (P. S. H.) pointed out in 1933. Mild jaundice should not be expected to provoke the analgesic phenomenon; perhaps even the moderate jaundice was not intense enough. However, it seems right to assume that the jaundice should have been intense enough in the 13 severe cases to provoke the phenomenon if this type of jaundice could invoke it. Perhaps this type of jaundice is different from others noted and, no matter how intense, cannot invoke analgesia. However, one of us (P. S. H.) met two British physicians who had noted isolated instances of rapid recovery from arthritis during "gold-jaundice." Further observations on this question, with estimations of serum bilirubin would seem of interest.—Ed.]

Of the patients of Hartfall, Garland and Goldie, 20 died: 10 from natural causes, seven from gold toxicity, three from unknown causes (mortality 0.8 per cent or, if the last three patients are included, 1 per cent). Deaths related to gold were as follows: three from purpura, one from agranulocytosis, two from hepatic necrosis, one from exfoliative dermatitis.

There was no certain way of preventing toxicity; the best way was to use small, properly spaced, doses. Reactions seemed more frequent among ambulatory patients; therefore hospitalization, at least during early doses, seemed advisable.<sup>150</sup> Parr and Shipton suggested that loss of gastric acidity favored reactions: 16 of 48 patients with low, or no, gastric acidity and only two of 22 patients with normal gastric acidity had reactions. Many physicians used liver extracts, calcium, glucose and ascorbic acid routinely but in individual cases these seemed useless to prevent or lessen toxicity. Some were impressed with the possibility that "patch tests" with gold might reveal sensitivity thereto.<sup>296</sup> If patients under treatment developed leukopenia further doses should be given cautiously. Eosinophilia or punctate basophilia, considered by some as signs of impending toxicity, were not noted by others.<sup>150</sup> The treatment of toxic reactions was entirely symptomatic. Use of gold was stopped at once. Liver extracts, sodium thiosulfate, calcium gluconate, ascorbic acid, increased intake of fluids seemed useful to some, useless to others.

In conclusion, Hartfall, Garland and Goldie who used gold alone in the treatment of their 750 patients, stated: "We firmly believe that rheumatoid arthritis if seen in its early stages can be cured by gold, and there are few

if any cases of the disease that cannot be improved." Others<sup>521</sup> concluded that the undoubted benefits from gold make it imperative to find a less toxic product or to learn how to minimize the toxicity of those now used.

*Vasodilators: Histamine, Choline.* Having observed physiologic reactions therefrom, several workers<sup>65, 446</sup> considered it proved that by iontophoresis, molecules of acetyl-beta-methyl choline could be transmitted into human tissues sufficiently to stimulate the parasympathetics. Boyd, Osborne and Markson treated 15 patients with "chronic infectious arthritis": pain was decreased in five, motion increased in six, fatigue decreased in six; many were not improved. Of 36 patients with "infectious arthritis" treated similarly by Martin and Eaton, 57 per cent were "helped," "some became symptom free." Kling and Sashin considered mecholyl iontophoresis much inferior to that with histamine. A procedure for using the latter at home was developed: of 42 patients, 71 per cent were "cured or improved"; 29 per cent not improved. Young recommended a histamine-containing ointment ("imadyl") for home use by patients: of 16 patients 11 were "markedly improved"; five had little or no improvement.

[Probably these methods provide transient subjective relief but results have not been impressive; no adequate comparison between this and ordinary physiotherapy has been made to our knowledge.—Ed.]

*Sulfanilamide.* In the early work with the prontosils a few patients with "infectious arthritis" were treated with presumed benefit.<sup>424</sup> Veil (1933) noted marked improvement from prontosil I in a case of "rheumatism" or "polyarthritis." A few patients with "chronic infectious arthritis" treated by Gantenberg and Thimme (1935) were reputedly benefited. "Arthritis deformans" was reported as successfully treated with sulfanilamide by Ory (1936). Mitchell and Trachsler noted the death from agranulocytosis of a child with Still's disease given prontylin (dose and duration unstated). A patient of Brown, Bannick and Habein with an acute exacerbation of chronic atrophic arthritis developed hemolytic streptococcal septicemia; prontosil II and sulfanilamide cured the latter but did not affect the joints. Results in a few cases of atrophic arthritis were "questionable."

[No study on the effects of sulfanilamide in a significant number of cases of atrophic arthritis has yet appeared but one by Bauer and Coggeshall soon will. One of us (P. S. H.) has treated several patients, with disappointing results and with marked toxicity in a few, with severe, nonfatal agranulocytosis in one, and with prolonged fever in two.—Ed.]

*Rest and Movement.* The problem for arthritics should not be one of "rest *versus* exercise" but "rest *and* exercise" and not too much of either; not so much rest as to permit ankylosis and not so much exercise as to keep up inflammation. Many laymen and physicians believe that joints must be rather constantly moved to prevent ankylosis; for the latter, exercises in bed or a complete range of motion of affected joints a few times

daily will suffice. Complete rest in bed for three to six weeks was advised in early or severe cases when possible; otherwise reduction of as much occupational trauma as possible.<sup>282, 322, 389, 514, 545</sup>

*Physical Therapy.* Physicians may argue the merits of other forms of therapy but they agree on the value of physical therapy although they may express preference for one or another form. The cost of their disease is so great that patients must be allowed, and instructed, how to use simple methods of *home physical therapy* to supplement professional service; these were described.<sup>282, 545</sup> The indications for, technic, and relative merits of the common forms of physical therapy were given; the importance of correct body mechanics was stressed.<sup>292, 389, 391, 632, 715</sup> For hands and feet, melted paraffin baths are most useful.<sup>545, 661</sup> The biologic action of infra-red, luminous and ultraviolet light and their indications were reviewed.<sup>209</sup> The merits of electrotherapy,<sup>392</sup> hydrotherapy<sup>682, 742</sup> and Pistany mud packs<sup>495</sup> were noted.

Arguments on the relative merits of short wave diathermy and of ordinary (long wave-) diathermy were continued. Dalton championed the view that short waves have a specific effect unrelated to their heat production, a view rejected by the majority, who believe that claims to superiority of short wave diathermy are mostly fallacious. The main effect of both short and long waves is from heating and no superior or specific action of short waves has been proved.<sup>51, 161, 163, 171, 390</sup> However, short wave therapy has certain technical advantages over long wave diathermy; for the former no direct contact of metal and patient is required, a useful fact in treating tender, inflamed regions. The clinical application of short wave therapy was discussed<sup>336, 553</sup>; it seemed more valuable in atrophic arthritis and fibrositis than in hypertrophic arthritis or sciatica.<sup>855</sup>

The aims and methods of the English spas and the indications for immersion baths, manipulation pool baths, massage-douche baths, vapor baths and mud packs were noted (Thomson). In one way or another all the waters promote elimination, "one of the most important factors in the spa treatment of rheumatic diseases." Spa therapy is not practical in acute gout, and is of "very doubtful value" if severe fever accompanies chronic atrophic arthritis.<sup>678</sup> The facilities of a physical therapy clinic for London bus men were described.<sup>661</sup> Although there are more than 8000 mineral springs in the United States, there are only 20 or 30 American spas; these were listed and the work of the Saratoga Spa was described by McClellan. The education of American medical students in physical medicine, including roentgen-rays and radium, is very meager; in 60 accredited medical schools an average total of only five hours is devoted thereto (Lowry). Entrance requirements for the 14 approved American schools for physical therapy technicians were noted.<sup>155</sup> Brown outlined the organization of a teaching clinic for physical therapy. It behooves physicians to learn the general principles of physical therapy so that they can properly prescribe physical treatments for patients rather than to leave the prescription of massage and exercises to

"the gambling instincts of the technician" (Hansson). Criteria by which the Council on Physical Therapy adjudges apparatus or forms of physical therapy for Council acceptance were discussed.<sup>162</sup> The history of physical medicine was briefly outlined by Rolleston.

*Occupational Therapy.* Whenever possible, occupational therapy should be prescribed as an important part of treatment for arthritic patients (Pattee). It should be closely integrated with physical therapy. Occupational therapists use a variety of methods applicable in all but acute cases. These methods, many of which can be used at home, can do much to restore muscle tone and joint mobility, and to increase the patient's confidence that useful articular function can be regained.

*Roentgen-Rays and Radium.* Opinions differ as to the value of roentgenotherapy for chronic arthritis (Fineman). A few recent writers have reported an analgesic (but rarely a "curative") effect in hypertrophic, more often than in atrophic, arthritis. Some writers noted some, others no, significant results in atrophic arthritis or spondylitis. Kahlmeter summarized 12 years' experience with roentgenotherapy in 4000 rheumatic cases and gave his plan of treatment for each type. It was much less effective in atrophic arthritis than in other types. Its effect on periarticular inflammation was beneficial; that on intra-articular disease was of "exceedingly slight value"; no significant effect on destroyed cartilage or chronic intra-articular exudates can be expected. Hernaman-Johnson also concluded that roentgenotherapy to individual joints may give some temporary relief but does not affect progress of the disease.

Ingestion of radon in doses of from 80,000 to 240,000 Mache units gave no relief to patients with atrophic arthritis (or with hypertrophic arthritis, fibrositis or neuritis) (Howitt, Pillman-Williams and Russ).

*Fever Therapy.* Results of fever therapy were not impressive; they were naturally somewhat better in acute and subacute, than in chronic, atrophic arthritis. Most workers concluded that fever therapy should be used only as an adjunct to other therapy; it may provide some temporary analgesia, but recurrences were common.

Of 20 patients with acute rheumatoid arthritis treated by Stecher and Solomon, 12 (60 per cent) received "prompt relief and apparent cure"; eight (40 per cent), partial relief. The course of the disease was "favorably modified in every case." Sessions of fever were each four to five hours at about 105° F.; two to six sessions were given. Bierman's results were also better in acute than in chronic cases. Of 41 patients (acute and chronic), 50 per cent noted some definite and "permanent" improvement. In most of the chronic cases relief was only temporary. Of Shepard's eight patients seven were "definitely improved." Davidson and Warren tried to correlate clinical and roentgenologic improvement of 24 patients with "infectious arthritis" followed one to four years. Each patient received, apparently, only one session of fever (four hours at 40.5° C.) but a "hot bath routine" intermittently thereafter. Results were "failure" in three cases with no clinical or roentgenologic improvement and in six cases with temporary clinical but no roentgenologic improvement (total 38 per cent). In 15 cases there was clinical and roentgenologic improvement (recalcification of subchondral bone; increase in density and number

of bony trabeculae). [Clinical improvement can occur without roentgenologic improvement; indeed, after patients are clinically "cured," certain roentgenographic changes may continue to develop as the pathologic reactions initiated by inflammation "resolve" to their end-stage.—Ed.]

Of Brodribb's eight patients, four were permanently, four only temporarily, improved by fever therapy. Seven patients of Speker and McBryde and four of Williams, with atrophic arthritis, were only temporarily benefited. But results were much better in 10 cases which Williams called "chronic arthritis." Schnabel and Fetter noted the following: Of 17 chronic cases, little or no improvement in nine, moderate but only temporary improvement in eight. In six acute or subacute cases, notable relief lasted in only two. Simmons used fever as adjunct therapy for 36 patients: 78 per cent were improved; hence, fever therapy was considered valuable.

[So many measures were used that results of any one cannot be evaluated.—Ed.]

*Climate.* It has not been proved that residence in a warm, dry climate improves a patient's prognosis; if his environmental factors are the same, he may be as well off at home (Miller). In one Boston hospital rheumatic patients noted considerable symptomatic relief when the humidity of their rooms was stabilized by air conditioning.<sup>745</sup>

*Sympathectomy.* Most writers<sup>606, 716, 717</sup> no longer consider sympathectomy suitable treatment for arthritis. Adson recommended it only when atrophic arthritis is associated with marked annoying vasospastic phenomena. Reviewing reported results, Learmonth concluded that sympathectomy may modify the pain but not the course of the disease and that the variability in its results argues against the view that arthritis is due to impoverished circulation. Corbin performed lumbar sympathectomy on several cats; two years later there were no significant gross or microscopic changes in bones or joints. On other cats both lumbar sympathectomy and lumbar and sacral deafferentation were done; thereafter the deafferented limbs were usually carried in a position of extension and either abduction or adduction. In the next one to three years, arthritic changes like those of *malum coxae senilis* (degeneration and erosion of cartilage, eburnation, bone hypertrophy, some synovial hyperplasia) developed in deafferented hip joints, changes believed to be due to diminished articular sensibility.

[Could they have resulted from trauma alone; from use of limbs in markedly abnormal positions?—Ed.]

*Orthopedic Methods for Prevention and Correction of Deformities.* Nonsurgical methods. Correction of deformities too often consists of "the correction of mistakes made by doctor or patient."<sup>322</sup> However, such great strides have been made that even when deformities are present, no longer is the deformed cripple an outcast from the big hospital and doomed to a life of hopeless crippledom.<sup>681</sup> Deformities are generally due to muscle spasm followed by capsular shortening and intra-articular changes. Muscle spasm often can be corrected by simple rest<sup>322, 666</sup>; if this is inadequate, splints or casts can be used. Some preferred to apply one, or a series, of light metal (duralumin) splints or light plaster shells to correct or prevent deformity.<sup>238, 322, 373, 417, 545, 666</sup> Some medical supply houses now put up plaster bandages, in neat packages, ready for instant use. Plaster bandages are es-



pecially useful for wrists, knees and shoulders. If ankylosis is impending, joints should be placed in an optimal position for future function. These positions were again described.<sup>238</sup> The prolonged application of plaster casts fosters deformities; if casts are used they must soon be bivalved.<sup>238</sup> Extension by weights is indicated for certain joints, especially hips.<sup>238</sup> Some<sup>333</sup> considered manipulation of joints under anesthesia generally dangerous; others approved it in suitable cases (with disease not active in any joint). The hazards of postponing manipulation too long may be greater than doing it "too early" when slight inflammatory activity is still present.<sup>238, 322, 681</sup> Methods for correction of body mechanics were again described.<sup>238, 307, 666</sup> The management of painful arthritic feet by nonsurgical means (pads, bars, plastic foot support), and surgical means (tenotomy, metatarsal excision) was outlined.<sup>661, 676</sup> Bohlman recommended aspiration and injection of air into arthritic joints with exudates.

[There is no reason why medical men, especially those who do not have the services of an orthopedic colleague at hand, can't learn the simpler orthopedic procedures.—Ed.]

**Surgical methods.** General and special requirements of the various surgical procedures for correction of joint deformities were reviewed:<sup>238, 333, 681, 730</sup> The arthritis must (usually) be entirely quiescent for at least six months; the patient's physical and financial condition and morale must be sufficient to permit fulfillment of the (sometimes) long periods necessary for operation and subsequent observation; the expected functional gain must be worth the effort (Wilson). Indications for excision of joints were marked articular destruction and severe pain.<sup>238, 681</sup> Arthrodesis was recommended, especially for painful hips resistant to long treatment.<sup>238</sup> Osteotomy was recommended for joints, especially hips and shoulders, ankylosed in bad positions, or for flexion contractures with damaged joints and narrow joint spaces.<sup>730</sup> Arthroplasty was especially useful for ankylosed elbows, knees and hips.<sup>238, 378, 573</sup> Arthrotomy and lavage with Dakin's solution seemed valuable in resistant subacute arthritis of knees.<sup>238</sup> Removal of loose bodies is sometimes required to correct recurrent "locking."<sup>238</sup> In cases of chronic hyperplastic synovitis with effusion, synovectomy may be valuable.<sup>238, 730</sup> The use of posterior capsulotomy for correcting obstinate flexion deformities of knees, unrelieved by physical therapy, weights or splints, is spreading.<sup>238, 322, 786</sup> Usually this is done only in entirely quiescent cases but Littlefield obtained excellent results, even in the presence of mild clinical activity.

**Psychotherapy.** The value of psychotherapy as an adjunct to other treatment for arthritis, especially the atrophic type, is being increasingly appreciated. A certain amount of psychotherapy, consciously or unconsciously applied by the attending physician is essential to alleviate the despondency which these diseases engender.<sup>126, 672</sup> By a spirit of continued optimism and friendly encouragement, the physician, the clergyman, the family and friends of an arthritic patient all have their place in restoring the patient's self-confidence.<sup>545</sup>

(To be continued)

# CASE REPORT

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## FURTHER EVIDENCE IN REGARD TO FUNCTIONAL BUNDLE-BRANCH BLOCK \*

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It is the purpose of this presentation to add some further evidence in regard to the occurrence of functional bundle-branch block. I shall attempt to do so by a partial review of the literature, the presentation of a case report and consideration of some of the mechanisms which may be responsible for this abnormality. Strictly speaking, the term "functional bundle-branch block" should be restricted to those instances in which there is no organic basis either temporary or permanent for the production of the conduction disturbance. In general, however, the literature has dealt with transient or temporary bundle-branch block and functional bundle-branch block as synonymous terms. Therefore, certain examples of transient bundle-branch block have been included.

The electrocardiograph has added greatly to our knowledge of the heart and the instrument is indeed indispensable in the practice of cardiology today. Cardiologists have been most eager to present the evidence which indicates the value of the instrument. We have, however, been less inclined, perhaps, to elaborate on instances in which the electrocardiogram may, in fact, be misleading because of the imperfection in our knowledge of its interpretation. Some few years ago we considered the so-called coronary T-wave as pathognomonic of coronary closure. Gradually, however, experience has taught us that other conditions may produce similar T-wave changes. We now view the electrocardiographic changes more correctly as only one link in the chain of evidence. In like manner, it has taken time for us to discover the full facts about other electrocardiographic findings. Until very recently it was generally accepted that the electrocardiographic picture of bundle-branch block always carried a very grave prognosis, being always indicative of serious organic heart disease. The fact that one would be right in such an interpretation in the vast majority of instances does not in anyway lessen the tragedy of offering such a prognosis to even one individual for whom it was not correct. We cannot rightly excuse such a mistake on the grounds that we were confronted with an unusual or rare finding. It happens that so far as the individual under consideration is concerned, this "rare" finding is the only one of significance.

### REVIEW OF LITERATURE

Even a partial review of the literature indicates that evidence of transient and functional bundle-branch block has been accumulating for many years. As early as 1913, Lewis<sup>1</sup> found a case in which transient bundle-branch block occurred during an acute febrile attack. However, Hermann and Ashman<sup>2</sup> have called

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attention to the fact that the electrocardiographic curves in this case would now be considered highly suggestive of coronary disease. In this instance, therefore, we might readily suspect that temporarily, at least, there was an organic cause for the bundle-branch block. In 1915, Wilson<sup>3</sup> reported a case which would more correctly be termed "functional" bundle-branch block. He states: "The normal rhythm when spontaneously present could be converted into an atrioventricular rhythm with right bundle-branch block by indirect or direct stimulation of the vagus nerve, and the abnormal rhythm, when spontaneously present, could be converted into the normal rhythm, by the administration of atropine in doses sufficiently large to paralyze the vagi." Robinson<sup>4</sup> in 1916 reported a case in which the defective intraventricular conduction was clearly not based on pathologic lesions. He advanced the theory that the interference with conduction was due to "functional fatigue." Willius and Keith<sup>5</sup> in 1927 cited three cases of intermittent bundle-branch block. Each had evidence of myocardial disease. The authors explained the conduction disturbance on the basis of myocardial fatigue. In two of the three cases the disturbance was present only during cardiac failure. Baker<sup>6</sup> in 1930 reported a case in which bundle-branch block appeared whenever the cardiac rate was high and disappeared when the rate decreased. He interprets this to mean that the reduction in duration of the cardiac rest period, accompanying the increased rate, caused the intracardiac circulation to become temporarily inadequate to maintain the normal functioning of the bundle of His. Anoxemia of the conducting tissues was therefore the mechanism responsible for the conduction defect. In proof of this it was observed that during artificial administration of oxygen an increase in heart rate did not cause bundle-branch block. Baker cites, also, the fact that Lewis and Resnik had previously demonstrated that in some instances simple asphyxia affects the intraventricular conduction, and that others had observed bundle-branch block to diminish in degree following the administration of oxygen.

In 1930, Wolff, Parkinson and White<sup>7</sup> made a most important contribution when they reported a series of 11 cases in which they observed bundle-branch block and short P-R intervals in healthy young people who were prone to have paroxysmal tachycardia. It was observed in several of these cases that whenever the P-R interval increased spontaneously to normal, or in response to exercise became normal, then the bundle-branch block configuration disappeared. Likewise, in one instance (Case 1) the administration of atropine restored the complexes to normal and increased the P-R interval from 0.1 second to 0.15 second. The authors interpreted their findings as indicating that a strong vagal influence was responsible for the displacement of the normal pacemaker in the auricle and also for inhibition of one branch of the bundle of His with resulting bundle-branch block. In 1933 Wolferth and Wood,<sup>8</sup> noting that complexes such as those described by Wolff, Parkinson and White are observed once in every one thousand electrocardiographic examinations, sought to explain the mechanism on the hypothesis of an accessory pathway of auriculo-ventricular conduction such as was described by Kent<sup>9</sup> between the right auricle and right ventricle. This hypothesis has received, however, very little support.

Hermann and Ashman<sup>2</sup> in 1931 reviewed the cases of transient bundle-branch block that had appeared up to that date and presented eight cases of their own. They emphasized the fact that in most of the presented cases the transi-

tion from normal conduction to defective intraventricular conduction has been a gradual process, and in most of these myocardial exhaustion and anoxemia, functional fatigue, the accumulation of products of cell metabolism and congestive heart failure were precipitating causes. In three of their own cases, however, the transition from the normal electrocardiogram to that of bundle-branch block occurred abruptly. These three cases are of particular interest. In Case 1, indirect vagus stimulation by deep inspiration would cause a sudden change from bundle-branch block to normal curves. It was observed also that coincidentally the heart rate always decreased from about 75 to 65 beats per minute. Also curves taken after prolonged rest showed normal conduction, whereas slight exertion caused the bundle-branch block configuration to reappear. Although it was not stated that this patient had definite organic heart disease, it seems most likely that anoxemia of the conducting tissue or "functional fatigue" caused the block, and that the improvement observed following vagus stimulation was due to the "slowing of the heart rate," with consequent relief of the anoxemia. In the other two cases definite organic heart disease was present. In Case 2, after slight exertion, normal complexes could be produced by indirect vagus stimulation, although the heart rate altered little. Here again, the relief of bundle-branch block by rest in bed indicates the effect of "functional fatigue." In Case 3, also, periods of normal conduction were observed to follow prolonged rest.

In 1932, Elliott and Nuzum<sup>10</sup> reported a case of unusual interest. Their patient's electrocardiogram showed a predominant bundle-branch block configuration. There were a few normal appearing complexes. During a short period of two to one auriculo-ventricular block when the ventricular rate was markedly slow the bundle-branch block disappeared. As soon, however, as the auriculo-ventricular block disappeared and the ventricular rate increased to normal, there was a return of bundle-branch block. In response to vagus stimulation, the auricular rate could be slowed, and the bundle-branch block configuration again disappeared. In 1932, also, Morris and McGuire<sup>11</sup> reported two patients in whom cardiac symptoms came on acutely and in whom the electrocardiogram demonstrated transient bundle-branch block. In the first of these cases acute pulmonary edema and a state of shock were present at the time the bundle-branch block curves were taken. In the second case, likewise, there was a state of collapse with very low blood pressure during the time that bundle-branch block was demonstrated. These cases, then, like that of Baker, were presumably due to temporary inadequacy of the intracardiac circulation to the bundle of His. Carr<sup>12</sup> in 1933 also reported transient bundle-branch block which accompanied an acute cardiac incompetency. In 1934 Willius and Anderson<sup>13</sup> reported a case of transient recurrent bundle-branch block. Complexes with normal conduction were often followed in 24 hours by those showing bundle-branch block, although, clinically, the patient was unchanged. Their patient was a hypertensive and also in the age group where coronary disease is common and, therefore, they explain the phenomenon on the basis of transient recurrent disturbance in the circulation, affecting the bundle.

Tung<sup>14</sup> in 1936 reported two additional cases of the type previously described by Wolff, Parkinson and White. Two healthy young Chinese, who were subject to attacks of paroxysmal tachycardia, presented between attacks electrocardiograms characteristic of bundle-branch block with a short P-R interval.

He also had observed, but did not report in detail, three other individuals whose electrocardiograms presented a similar characteristic, but who were not subject to paroxysmal tachycardia. In Case 1 of his report, administration of one milligram of atropine caused a gradual reversion to normal ventricular complexes with a normal axis, although the P-R interval continued short. In the second case, atropine (2 milligrams) had no effect. Kurtz<sup>15</sup> in 1936 reported six cases of transient bundle-branch block. In each case, there was, however, advanced organic heart disease. He felt that the block was due to disturbance of circulation and nutrition of the conduction tissue.

#### CASE REPORT

Mr. J. W. B., aged 59 years, was first seen on April 24, 1936, complaining of recurrent attacks of palpitation of six years' duration.

His family history was negative except for tuberculosis in his mother, who died at the age of 60 years. There was no history of cardiovascular disease in the family.

He had worked as a furniture salesman for 38 years, traveling a rather wide territory. He denied all previous illness except arthritis of the shoulders, which was relieved in 1929, by extraction of his teeth. In 1934, an automobile accident resulted in fracture of the body of the fourth lumbar vertebra with consequent deformity and slight disability.

He stated that in 1930, for the first time, he had an attack of palpitation, which was sudden in onset, lasted one hour and ended abruptly following an injection by his physician. In 1933, another attack of the same character lasted about three hours and subsided without medical treatment. From that date until one week prior to my first observation he had several attacks of very short duration that required no treatment. Between attacks he was entirely free of all cardiorespiratory symptoms and worked quite hard. His last attack occurred one week prior to the present examination. He awakened one morning with a sense of palpitation, smothering, weakness and apprehension. The former was so severe that he called a physician, who gave him a hypodermic. The attack ended abruptly some five or six hours after onset.

Physical examination showed an elderly man, whose development and nutrition were good. His temperature, pulse and respirations were normal. The findings of importance were as follows: There was moderate retinal arteriosclerosis. The thyroid was not enlarged and there were no abnormal masses in the neck. There was likewise no abnormal pulsation or venous engorgement in the neck. The lungs were normal throughout. The cardiac impulse was not seen or felt. Percussion showed the heart not to be enlarged. The heart sounds were of normal character and no murmurs were present. The heart rate was 70, the rhythm regular. Blood pressure was 128 systolic and 80 diastolic. The abdomen was negative. The extremities were likewise negative. The diagnosis was paroxysmal auricular tachycardia.

The electrocardiogram in the three standard leads (figure 1) showed relatively low amplitude of the Q.R.S. complex, the maximum being six millimeters in Lead I. There was a left axis deviation and the P-R interval was 0.18 second. The Q.R.S. interval was 0.08 second. Being much interested in the carotid sinus reflex, I decided to test its effect on this patient. All tests of carotid pressure were made in Standard Lead II. Pressure on the right carotid (figure 2) did not change the form of the ventricular complexes nor alter the P-R interval. However, there was marked slowing of the heart, the R-R interval increasing from 0.9 second to 1.12 second. With subsidence of the effect, the rate slowly increased and the R-R interval became 1.04 seconds. Following left carotid pressure two different types of response were obtained (figure 2). On the first trial there was complete inhibition of the ventricles

for a period of six seconds. There was marked slowing also of the auricle, the P-P interval increasing gradually from 0.9 second before carotid pressure to a maximum of 1.26 seconds during carotid pressure. As the reflex subsided the ventricular complexes returned and followed the P-wave normally. The second attempt with left carotid pressure (figure 2) produced results at first similar to those following right carotid pressure, but after the pressure was continued for 4.6 seconds the ventricular

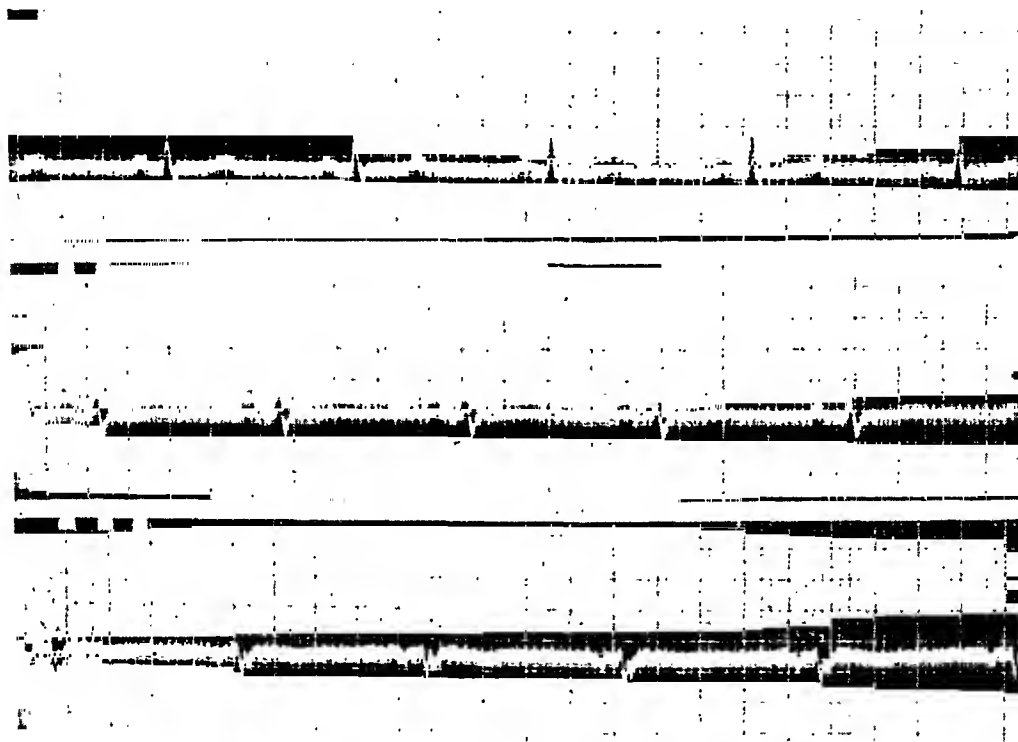


FIG. 1. Three standard leads.

complexes suddenly took on the characteristics of bundle-branch block, which were maintained for three heart cycles, the complexes being exactly equally spaced and at intervals of 1.4 seconds. There was then an abrupt return to normal complexes. The patient had experienced slight dizziness during both tests of left carotid pressure but subsequently felt entirely normal. He has continued well and required no treatment.

#### DISCUSSION

There is no doubt that we have sufficient evidence to the effect that bundle-branch block may be due to causes other than serious heart disease and also that it may be a transient or functional phenomenon. The literature indicates three chief possible mechanisms for such phenomena. First, bundle-branch block may be due to "functional fatigue." In such instances, the intracardiac circulation to the bundle of His is inadequate and it appears that progressive myocardial exhaustion and anoxemia, accumulation of products of cell metabolism and congestive failure are the cause of the bundle-branch block. Most of the cases observed in the literature have fallen clearly under this grouping. In such cases

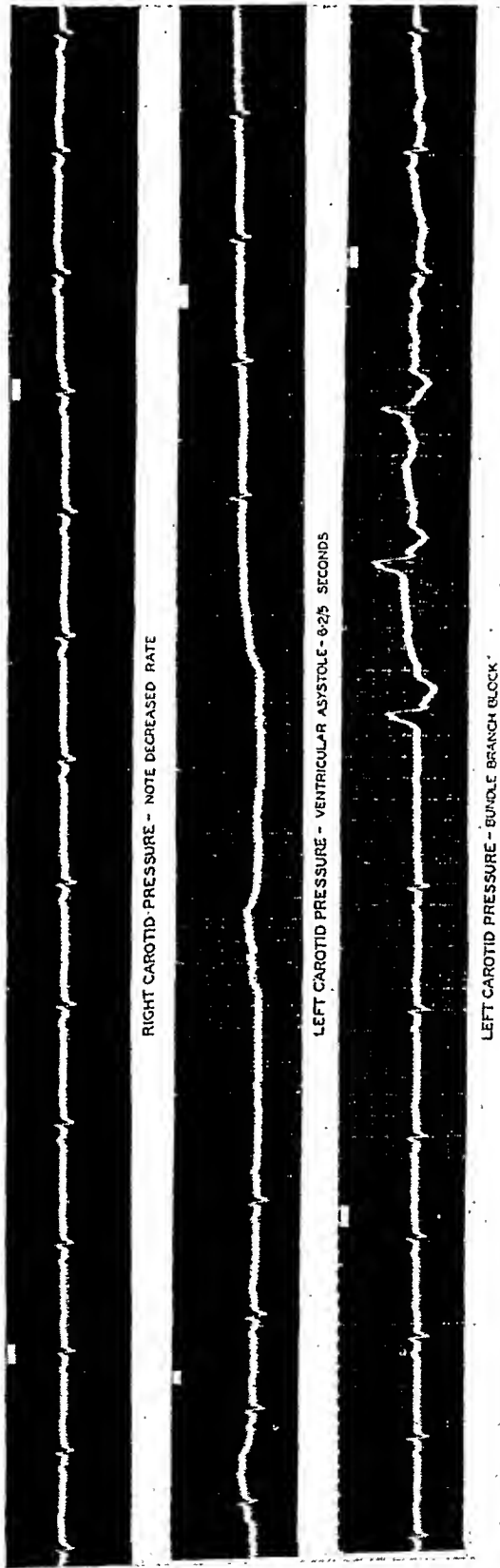


FIG. 2. All tracings in Lead II. The lead marker indicates beginning and end of all carotid pressures.

there is definite and usually serious heart disease, but periods of normal conduction may occur as the intracardiac circulation through the bundle improves as the heart rate is slowed by various methods, such as rest, medication or vagus stimulation. Second, it appears possible from studies of comparative anatomy that curves suggesting bundle-branch block may be due to abnormally rapid conduction of the cardiac impulse from right auricle to right ventricle by way of an accessory bundle of conductive tissue, the bundle of Kent. There has, as yet, been no demonstration of this pathology in a case which presented the abnormal electrocardiogram and, in fact, the proponents of this hypothesis admit that they have no direct proof of it.

Third, it is apparent that bundle-branch block may be due to increased vagus effect. This would seem to be the logical explanation for a number of cases which are observed in the literature, particularly those of Wolff, Parkinson and White, and also is the means of explaining the findings in the case here reported. In this case we clearly have evidence of a highly-active carotid sinus reflex which, in one instance, caused complete inhibition of the ventricle and later manifest its inhibition unequally on the two main divisions of the bundle, thereby causing bundle-branch block. The vagus effect here was clearly one of direct action on the conducting tissue and not due to any alteration in heart rate. It is apparent that in those instances of bundle-branch block due to functional fatigue, vagus stimulation may relieve the block by means of slowing the heart rate and improving the circulation to the bundle, whereas, in another instance, vagus effect may be the cause of bundle-branch block because this effect is manifest unequally on the two divisions of the bundle of His.

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## EDITORIAL

### *A RESEARCH CLEARING HOUSE IN THE MEDICAL SCIENCES*

Medical research has not often been benefited by ideas picked up from literary scholarship, but an excellent one is now knocking at our door. It can be seen in practical form in a publication, edited by James M. Osborn, formerly at Oxford but now at Yale, and issued by the Modern Humanities Research Association. This is an international organization for the advancement of literary research, with headquarters at Oxford. Called *Work In Progress*, their publication lists over two thousand separate projects now in the hands of literary scholars.

The purpose of their publication is to serve as a clearing house, making it possible for research workers all over the world to know what other researchers are doing. The success of the Editor in gathering information is demonstrated on every page by the wide range of universities whose work is reported. To select an example at random, the following distribution is observed on a single page from the section on French literature of the nineteenth century: Yale, Aix-en-Provence, London, Rome, Pecs (Hungary), Ohio State, Bryn Mawr, Budapest, Wisconsin, Pennsylvania, Strasbourg, Griefswald, Genoa, Lille and Harvard. Only through the medium of a clearing house can these workers in common or related fields be known to each other.

Medical research is being carried on in even more widely flung centers. Again and again medical history has demonstrated that important discoveries have no regard for geography. No one institution or single country can afford to disregard parallel investigations being carried on elsewhere, for there can be no isolation in medicine. A clearing house for medical research is, therefore, long overdue.

Three principal functions should be visualized for an agency of this kind. The first has already been touched on: To serve as a means of making known to each other, research workers of similar interests so that they can communicate whenever it may be desirable. For example, M. Blanc in Paris may have been experimenting with the host function of the cockroach at the same time Dr. Green in St. Louis may be seeking to establish a connection between cockroaches and influenza, and in Buenos Aires Dr. Royá may be observing the same insect in connection with cancer research. Obviously some simple, dependable, up-to-date and accessible method is needed to help these men to exchange information if they so desire. Few discoveries of any magnitude or importance have been completed without obligations to other minds. Furthermore as specialization increases an early exchange of ideas becomes imperative.

The second function of such a clearing house is to expose 'non-purposive' duplication where it already exists, and diminish its frequency in the future. Every veteran of the laboratory is familiar with examples of the gross wastage caused by such duplication. There are some occasions, quite naturally, when such duplication is justifiable and even desirable, provided it is undertaken deliberately and with the knowledge of those directly concerned. But blind duplication, of which there have been many unfortunate instances is inexcusable in this era of efficiency. Moreover at a time when research grants are tending to diminish it is especially important to use every dollar wisely. Money employed in duplicated research is too often money wasted.

The third function of the proposed clearing house should be directed toward the allocation of certain lines of research so that there will be as few blind spots as possible in a research program. It is very easy and tempting, as most investigators will attest, to be led off on a tangent and ultimately to abandon the original concept. But by a prearranged plan aimed at dovetailing research results so that when completed the sum of all the parts will equal the whole, much lost motion, money and time will be prevented. In this respect medical science could learn much from research methods used by the General Motor's Research Corporation under the directorship of Doctor Kettering. Several years ago, this greatest of engineers told me about a method he was then using in the study of combustion in motor engines, a program which on first thought seems far afield from mechanistic discovery. Thousands of corn seeds were planted. Every day as growth progressed the oxidative reactions of germination were critically studied. At the end of each week experts in physics, chemistry, biology and engineering met the combustion investigators and offered suggestions and criticisms of their work. By this plan the researchers were kept in the straight and narrow way of their quest and much waste of time and effort was avoided by not studying remotely related, though interesting side reactions. If such a method were adopted in planning a cancer research program the solving of the cancer enigma might be greatly accelerated.

In urging these considerations I have based my arguments on the practical necessity of conserving time, money and energy. But as scientists we must not overlook the fundamental fact that most of our advances have been due to the application of an orderly plan of work, what we refer to as *the scientific method*. This method begins with careful observations, proceeds by checking the conclusions with experiments, and then pours the tabulated experience into the great common fund of knowledge from which we draw as required. The public calls this fund of facts "science," but we know that science is not a body of knowledge, but the method by which facts can be established. The last important extension of the scientific method was the development of systematic bibliography, which enables a researcher, who wishes to pursue a specialized subject, to place his fingers immediately on material already written on that subject.

And now the scientific method is ready for the next step, which is to utilize a clearing house that will enable researchers, if they so desire, to communicate with others *before publication*. Knowing what *has been done* is not enough; communication should be made possible while an experiment is under contemplation or in progress.

The details of organizing a clearing house to serve medical research can be easily worked out. Each country could have a subsidiary clearing house but a 'medical generalissimo' with a central clearing house should be the research director-in-chief. In their publication, *Work In Progress*, the literary people have decided on the printed list, which for their purpose is cheaper and more useful than a central bureau where card files and other records are maintained. For medicine a combination of both procedures might be desirable, a central office with a medically trained director who would also edit an annual list of *Medical Research in Progress*. The cost of its maintenance, a few thousand dollars, would be paltry indeed compared to the benefits it could bring about. One point which would have to be threshed out in advance is the extent to which this clearing house would serve as a "register," or device for staking out claims to areas of research. In principle, there should be no monopolies in medicine, no one should have prior right to any cure or technic where life and death are involved. Yet there may be instances where a research worker deserves some protection until his discoveries are ready to be announced. In these exceptional cases no report would appear in the published list or some procedure could be developed similar to the "preliminary reports" which are now found in medical journals. Details such as these can readily be worked out.

In connection with the above discussion it is very interesting to note that a National Council on medical education, licensure and hospitals, to serve as a "central clearing house" for existing groups concerned with the educational needs of American medicine, has been recently proposed by Dean Willard C. Rappleye of the College of Physicians and Surgeons at Columbia University.

Practical considerations demand, and scientific method requires that some kind of research clearing house be established. Great medical problems are yet unsolved, valuable human lives go prematurely over the precipice and we must have every tool easily available, which will help us in our work.

C. W. LIEB

## REVIEWS

*The Endocrines in Obstetrics and Gynecology.* By RAPHAEL KURZROK, Ph.D., M.D. 488 pages; 23.5 × 15 cm. The Williams and Wilkins Company, Baltimore. 1937. Price, \$7.50.

It is gratifying that the author has covered these constantly changing subjects with an open mind, and that he calls attention to those phases in which much work yet remains to be done. This book, therefore, as well as any other book dealing with endocrinology, is not the final word, nor does the author claim it to be.

There are 30 chapters with an excellent bibliography appended to each. There follows an author and subject index. The book is in pleasing form with clear type. Numerous excellent microphotographs illuminate the text, while the graphic charts serve to illustrate the data.

After fundamental chapters on embryology, histology, physiology, and chemistry, there are chapters devoted to a detailed consideration of each of the hormones. The author then discusses such important and practical clinical problems as the disturbances of menstruation, tests for pregnancy, the climacteric, and cystic glandular hyperplasia of the endometrium. For the research worker the final chapter on methods of hormone assay will be particularly useful.

Of especial interest are the chapters which cover the history of the subject, menstruation, the physiology of the uterus, toxemias of pregnancy, and functional sterility.

Emphasis is placed throughout upon the interrelationships which exist between the endocrine glands; and experimental and clinical data are given due importance.

It is the reviewer's opinion that this book will be more useful as a reference than as a text. One also feels that the author writes much more convincingly and clearly of the clinical considerations than of the experimental and laboratory phases of his topic.

While typographical errors are present, and there is at times a somewhat confusing interchangeable use of terms designating groups of substances, the author, a well known clinical endocrinologist, has produced an interesting, useful, and readable book on this intricate subject.

J. E. S.

*The Fundamentals of Internal Medicine.* By WALLACE M. YATER, A.B., M.D., M.S. (in Medicine). 1021 pages; 25 × 17 cm. D. Appleton-Century Company, New York and London. 1938. Price, \$9.00.

In his introduction to this new text, Dr. Yater says that it is designed primarily for the introduction of students to the subject of internal medicine, presenting the minimum amount of knowledge of clinical medicine a medical student or general practitioner should have at his fingertips. Most of the subject matter has been written by Dr. Yater himself, but eleven other authors have also contributed.

The reader is impressed by the book's brevity, clearness, orderliness and lack of confusing overdiscussion. Introduction to the different sections are written so that manifestations of diseases may be correlated with others in the same general groups. Symptomatology and differential diagnosis are stressed by means of diagnostic tables, outlines, and grouping of symptoms that are common to certain classes of disease. Presentations, however, are not from symptomatic, but from etiologic and anatomic viewpoints.

The author has followed the English custom of including a chapter on diseases of the skin. There is also a short section on diseases of the ear by F. C. Schreiber,

and one on diseases of the eye, by J. A. Grear. These three unusual chapters are intended to correlate knowledge of these specialties with the subject of internal medicine.

Illustrations are used freely, and are uniformly excellent. The publishers should be congratulated on the roentgen-ray reproductions.

"Fundamentals of Internal Medicine" may be fully recommended to medical students. In the reviewer's opinion, it is a valuable addition to our teaching texts.

T. N. C.

*The Chemistry of the Amino Acids and Proteins.* Edited by CARL L. A. SCHMIDT, M.S., Ph.D. xxiv + 1031 pages; 17 × 26 cm. Charles C. Thomas, Springfield, Ill. 1938. Price, \$7.50.

The present treatise represents a coöperative effort on the part of Dr. Carl L. A. Schmidt, editor and chief contributor, and sixteen individuals whose scientific interests lie chiefly in the field of the amino acids and the proteins. There are few people who are so well qualified by training and experience to write on this subject as are the editor and his collaborators. Their chief purpose was to bring together the scattered literature on the chemistry of the amino acids and proteins and to emphasize the more fundamental data by presentation in the same graphic or tabular form as in the original literature. The resultant compendium admirably covers the requirements of advanced students and research specialists interested in this particular field.

Most of the chapters are excellent. The first parts of the book present a discussion of the constitution, synthesis, isolation, analysis, reactions, biochemistry and physical characteristics of the amino acids and proteins. Then follow chapters on the amphoteric properties, electrochemistry, membrane equilibria, thermodynamics, dipolar structure and solubility of the same. Brief chapters on the relation of proteins to immunity and nutrition bring to a conclusion this most excellent book. Throughout it is much of the original work of the editor and his colleagues. It is the most substantial and modern book on the subject and is replete with references to the original literature. The entire volume has an air of competence and authority which could come only from writers with personal experience in these fields.

While the chemistry of the amino acids and proteins is so complete it almost defies criticism, the book contains but few and brief references to the physiology and metabolism of these substances. It is primarily written from the point of view of the physical chemist. Hence the present volume will be of less interest and value to the clinical chemist or the physician. The print of the book is easy to read and well set and the reproductions of the numerous figures are most excellent. A satisfactory author and subject index is also included.

E. G. S.

*Diseases of the Blood and Atlas of Hematology.* By ROY R. KRACKE, M.D., and HORTENSE ELTON GARVER, M.S. 532 pages; 26.5 × 18 cm. J. B. Lippincott Company, Philadelphia. 1937. Price, \$15.00.

The authors have had the ambition to combine in one volume an atlas of hematology, a description of the cells of the blood in health and disease, a clinical description of the diseases of the blood and a manual of hematological technic. They have achieved this purpose within the compass of a volume of slightly over 500 pages. As an atlas the book is not an outstanding success. There are 44 colored plates which are reproductions of colored drawings from actual preparations. They are all of real value. The total number of cells shown, however, is not sufficient for an atlas and does not illustrate the many variations which are observed. In certain instances the reproductions are more diagrammatic than exact.

There is a well arranged and clearly written account of hematologic terminology, of the origin and development of blood cells and of their morphology. The description of the cells is quite concise and follows conventional lines.

The clinical descriptions of the blood diseases are all interesting and easily read. At times, as in the description of pernicious anemia, they seem somewhat abbreviated for the importance of the subject. The leukopenic diseases have always interested the senior author and it is only natural that this section should be fuller and more informative than others. The hypochromic anemias are likewise interestingly described. An unusual feature is the inclusion of a chapter on malaria.

The section on technic is a valuable one. The authors prefer slides to cover slips. A few line drawings in this section would have added to the clarity of some of the procedures.

All in all this is a volume which will hold its own in competition with the numerous recent books on hematology which have appeared in this country. It is an adequate monograph for the internist.

M. C. P.

*Marihuana: America's New Drug Problem—A Sociologic Question with Its Basic Explanation Dependent on Biologic and Medical Principles.* By ROBERT P. WALTON, Professor of Pharmacology, School of Medicine, University of Mississippi. 223 pages; 23.5 × 15.75 cm. J. B. Lippincott Company, Philadelphia. 1938. Price, \$3.00.

The author has collected the available data on the addiction to the narcotic principle contained in the leaves and flowering tops of the hemp plant. At present there is a wave of addiction to smoking of marihuana cigarettes in various parts of the United States, so that the topic is a timely one. The history of this addiction, the many names given to it, what is known of its present world prevalence are topics dealt with in an interesting way. Popular, literary and scientific accounts of the drug's effects are given at some length. Its relation to crimes of violence seems well established. Its aphrodisiac effects are apparently the exception rather than the rule. There is a botanical description of the American hemp plant, *Cannabis sativa* L., and pharmaceutical details connected with the preparations derived from the resin secreted by pluricellular hairs on the flowering tops. The subject of the therapeutic use of *Cannabis* is briefly dealt with.

The book is a valuable reference text for a subject of increasing social importance.

M. C. P

## COLLEGE NEWS NOTES

### GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following gifts to the College Library of publications by members:

#### *Books*

- Dr. Robert F. Loeb, F.A.C.P., New York City—"Martini's Principles and Practice of Physical Diagnosis";  
Dr. Willard F. Machle (Associate), Cincinnati—"Industrial Hygiene: A Handbook of Hygiene and Toxicology for Engineers and Plant Managers";  
Dr. David Riesman, F.A.C.P., Philadelphia—"Medicine in Modern Society";  
Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor—"Diseases of the Blood."

#### *Reprints*

- Dr. Walter L. Bierring, F.A.C.P., Des Moines, Iowa—1 reprint;  
Dr. Louis F. Bishop, Jr., F.A.C.P., New York City—2 reprints (in duplicate);  
Dr. Lucien Y. Dyrenforth (Associate), Jacksonville, Fla.—1 reprint;  
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;  
Dr. George M. Lewis, F.A.C.P., New York City—3 reprints;  
Dr. Bernard E. McGovern (Associate), San Fernando, Calif.—12 reprints;  
Dr. Hyman A. Slesinger (Associate), Windber, Pa.—4 reprints;  
Dr. Clyde A. Undine (Associate), Minneapolis, Minn.—1 reprint.

Among the most interesting additions to the College archives is a gift by Dr. Clement R. Jones, F.A.C.P., Pittsburgh, who has sent a bound volume of the "Transactions of the American Congress on Internal Medicine, 1916," being a detailed report of the annual congress of the College and the Congress, held in New York City, December 28-29, 1916. The volume also contains a copy of the Constitution and By-Laws of the Congress and a full list of the members of the Congress at that date. The American Congress on Internal Medicine was the affiliated organization through which the annual sessions of the American College of Physicians were organized and presented.

Dr. Jones also donated to the College archives Nos. 2 and 3 (July and November, 1920), Volume I, of the "Annals of Medicine," the first journal sponsored by the American College of Physicians. These journals each contain the full roster of members of the American College of Physicians and the American Congress on Internal Medicine. Besides containing a number of original articles, the journals carried a large number of abstracts of current literature.

Acknowledgment is also made of the receipt of a small book, "Palestine Today" by Elihu Grant, Stamford, Conn.

A very deeply appreciated gift to the College office was that of the Eighteenth Edition of Dorland's Illustrated Medical Dictionary, by the Publishers, W. B. Saunders Co., through Mr. J. A. Lutz, Sales Manager.

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### SECTIONAL MEETING, KANSAS MEMBERS

Under the Governorship of Dr. Thomas T. Holt, F.A.C.P., and with Dr. William C. Menninger, F.A.C.P., acting as host, Kansas Fellows and Associates held their annual sectional meeting at the Menninger Sanitarium, Topeka, Kan., November 4, with a good attendance and an excellent meeting. The program was as follows:



Starting at 10:00 a.m.

"Some Facts Concerning Gastric Acidity"—Dr. Philip W. Morgan, F.A.C.P., Emporia.

"Case Presentations:

1. Isolated Congenital Dextrocardia.

2. Ruptured Heart with Hemopericardium Following Coronary Occlusion"—Dr. Kenneth L. Druet (Associate), Salina.

"Headaches"—Dr. Norman Reider, Topeka.

Afternoon

"The Rôle of the Pituitary Gland in Clinical Medicine"—Dr. A. J. Revell (Associate), Pittsburgh.

"The Misuse of Digitalis"—Dr. Frank A. Trump, F.A.C.P., Ottawa.

"Gall Bladder Dysfunction"—Dr. Fred E. Angle, F.A.C.P., Kansas City.

"Case of Acute Idiopathic Hematoporphyria with Acute Ascending Paralysis"—Dr. Harold W. Palmer, F.A.C.P., Wichita.

"Cardiac Neuroses"—Dr. William C. Menninger, F.A.C.P., Topeka.

Luncheon was served at the Menninger Sanitarium; there was a social hour from five to six in the evening at the home of Dr. Menninger and dinner followed at the Jayhawk Hotel.

These sectional meetings are characterized by being partly scientific and partly social.

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#### SECTIONAL MEETING, KENTUCKY MEMBERS

Under the Governorship of Dr. C. W. Dowden, F.A.C.P., Fellows and Associates of the American College of Physicians from Kentucky held their annual meeting at Lexington, December 19, 1938. Thirty-five members were in attendance and the meeting was reported to be one of the finest in the six years that annual sectional meetings have been held in Kentucky. Kentucky was first, or certainly among the first, to hold these state meetings.

The program was as follows:

Starting at 3:00 p.m.

"Study of Glucose Tolerance Tests, Presentation of a Case of Diabetes Mellitus with Unusual Response to Insulin and Diet"—Dr. John W. Scott, F.A.C.P., and Dr. John Harvey, F.A.C.P.

"Tuberculous and Non-Tuberculous Tracheo-Bronchitis with Mediastinal Glands: Presentation of Two Cases"—Dr. Edward James Murray, F.A.C.P.

"Non-Tropical Sprue: Presentation of Two Cases"—Dr. Carl Hale Fortune, F.A.C.P.

Special Address on Angina Pectoris—Dr. William J. Kerr, F.A.C.P., President of the College.

A dinner followed in the evening at the LaFayette Hotel, given especially in honor of President Kerr. Dr. Carl Hale Fortune, F.A.C.P., was in charge of arrangements.

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Dr. LeRoy S. Peters, F.A.C.P., Governor of the College for New Mexico, Albuquerque, is the retiring president of the Southwestern Medical Association, embracing the States of Arizona, New Mexico, West Texas and Northern Mexico.

Dr. Howell Randolph, F.A.C.P., Phoenix, Ariz., is the incoming president of the above organization, and Dr. Orville E. Egbert, F.A.C.P., El Paso, Tex., is the president-elect.

Dr. Carl J. Wiggers, F.A.C.P., Cleveland, was honored by his associates at a surprise tea on the afternoon of November 23, 1938, to celebrate the twentieth anniversary of his appointment as Professor of Physiology at Western Reserve University School of Medicine. On this occasion, Dr. Wiggers was presented with a book of photographs and letters of appreciation from the President of the University, the Dean of the School of Medicine, members and former members of the staff of the Department of Physiology and students who had done special work under his tutelage.

Dr. Wiggers has recently returned from a lecture trip to South America, where he visited Callao, Peru; Arica; Valparaiso; and Santiago, Chile. His itinerary took him by plane over the Andes to Buenos Aires. Dr. Wiggers delivered a series of lectures in Spanish on the applications of physiology to medicine in Buenos Aires, Santa Rosa, Rosario and Coroba. Chief among these were addresses before the VIth National Congress of Medicine.

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Dr. August A. Werner, F.A.C.P., St. Louis, had an exhibit entitled "Theelin—Clinical Studies" before the scientific sections of the American Dental Association at St. Louis, Mo., October 24–28; the Interstate Post Graduate Medical Assembly at Philadelphia, October 31–November 4; and the Southern Medical Association at Oklahoma City, November 15–18.

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During November Dr. George Herrmann, F.A.C.P., Galveston, Tex., delivered addresses before the Clinical and Pathological Society of the University of Southern California, the California Heart Association (of which Dr. B. O. Raulston, F.A.C.P., is President) and the Los Angeles County Medical Association. His titles before the above-mentioned societies were, respectively: "The Chemical Nature of Heart Failure"; "Treatment of the Failing Heart"; "Criteria for the Diagnosis of Coronary Thrombosis and Some Suggestions on Its Treatment."

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Dr. Francis R. Dieuaide, F.A.C.P., is on leave from his post as professor of medicine and head of the department of medicine of the Peiping Union Medical College, Peiping, China, and spending the year as research associate in biological chemistry at Harvard University Medical School.

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Col. Charles F. Craig (MC), U. S. A., Retired, F.A.C.P., has been retired as Emeritus Professor of Tropical Medicine at Tulane University of Louisiana School of Medicine and is now occupying his new home at 239 W. Lullwood Ave., San Antonio, Tex.

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Dr. Z. Bercovitz, F.A.C.P., New York City, addressed the American Society of Tropical Medicine at Oklahoma City, November 15, on "The Differential Diagnosis of Amebic Dysentery from the Microscopic Examination of Bowel Discharges"; the Peoria Medical Society, at Peoria, Ill., November 21, on "The Diagnosis and Treatment of Chronic Ulcerative Colitis"; and the St. Louis Medical Society at St. Louis, November 22, on "The Diagnosis and Treatment of Chronic Ulcerative Colitis."

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Dr. Anthony Bassler, F.A.C.P., President of the National Gastro-enterological Association, and Dr. Samuel Weiss, F.A.C.P., Editor of the *Review of Gastro-enterology*, both of New York City, have been honored by the Italian Gastro-enterological Society (Italy), by being elected Honorary Fellows.

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Dr. Samuel M. Feinberg, F.A.C.P., Chicago, was the guest speaker at the discussion and meeting of the Oklahoma Allergists, November 17, 1938, held in connection with the Southern Medical Association. His subject was "Clinical Aspects of Mould Allergy."

Dr. Henry M. Moses, F.A.C.P., has been reelected Director of Medical Service at Kings County Hospital (Brooklyn). He is also Consultant in Medicine at the Wyckoff Heights Hospital (Brooklyn).

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Dr. A. J. Logie (Associate), Director, Division of Tuberculosis, Florida State Board of Health, participated in the scientific program of the Thomas County Medical Society, Thomasville, Ga., December 21, 1938, speaking upon "The Changing Picture of Tuberculosis."

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Dr. H. I. Spector (Associate), St. Louis, was elected President of the Mississippi Valley Conference on Tuberculosis at its recent annual meeting held in St. Louis.

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Dr. Hyman I. Goldstein (Associate), Camden, N. J., has been elected President of the Northern Medical Association of Philadelphia for 1939. The Association will begin its 93rd year, having been founded in 1846. It is one of the oldest medical societies in Pennsylvania.

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Dr. Frank S. Horvath, F.A.C.P., Washington, D. C., presented the following papers before the alumni of Georgetown University Medical School during the past autumn: "Unusual Electrocardiograms" and "Arterial Hypotension." Dr. Horvath addressed the George Washington Medical Society on November 19 on "Criteria for the Diagnosis of Mitral and Aortic Valvular Disease." The murmurs were demonstrated by the electric stethoscope and amplified.

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The Fourth Annual Postgraduate Institute of The Philadelphia County Medical Society will be held March 13-17, inclusive, 1939. The subjects to be considered are those embraced by the terms "Blood Dyscrasias" and "Metabolic Disorders." These will be further subdivided for convenience in instruction into eighty-six clinical lectures, with open forum discussion for each topic, delivered by as many individual specialists of national distinction.

Dr. Rufus S. Reeves, F.A.C.P., is the Director of the Postgraduate Institute and President-Elect of the Society.

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Dr. Ralph Pemberton, F.A.C.P., Philadelphia, addressed the Pittsburgh Academy of Medicine, December 13, 1938, on "The Syndrome of Arthritis."

Duke Hospital, at Durham, N. C., has just announced plans for a new 200-room addition to the present hospital building, providing from 100 to 120 new beds and raising the total capacity of the hospital to more than 550 beds. The new addition will provide for the expansion of the Hospital's clinic services. During the past two years there has been an almost constant waiting list of patients at Duke Hospital from every county in the State as well as from outside states. The addition will utilize the latest developments in mechanical and electrical equipment and in its arrangement.

A number of Fellows of the American College of Physicians are active on the Faculty of the Medical School and on the Staff of the Hospital. At the main entrance to the Duke Hospital the seals of the American College of Physicians and of the American College of Surgeons are sculptured in the stonework on either side.

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Louis F. Bishop, Jr., M.D., spoke on "The Management of Coronary Artery Disease" before the Waterbury Medical Association at Waterbury, Connecticut, on Thursday, December 8. Dr. Bishop also spoke at the Goshen Hospital on December 6, on "Electrocardiograms in Heart Disease."

## NEW ELECTIONS TO COLLEGE MEMBERSHIP

At a meeting of the Board of Regents December 18, 1938, at the headquarters building, Philadelphia, the following candidates were regularly elected to the class indicated:

## ELECTIONS TO FELLOWSHIP

December 18, 1938

<i>Candidates</i>	<i>Sponsors</i>
<b>ALABAMA</b>	
Marion Tabb Davidson, Birmingham	Seale Harris, James S. McLester, Groesbeck Walsh, Fred Wilkerson
Edgar Gilmore Givhan, Jr., Birmingham	James S. McLester, Joseph E. Hirsh, Fred Wilkerson
James Bowron McLester, Birmingham	James E. Paullin, Joseph E. Hirsh, Fred Wilkerson
<b>ARIZONA</b>	
Jesse Dewey Hamer, Phoenix	W. Warner Watkins, Harlan P. Mills, Fred G. Holmes
<b>CALIFORNIA</b>	
Joe Edmund Walker, Long Beach	Noel F. Shambaugh, Fred B. Clarkc, James F. Churchill
Leland Potts Hawkins, Los Angeles	Carl R. Howson, Raymond G. Taylor, James F. Churchill
Mast Wolfson, Monterey	Arthur L. Bloomfield, Thomas Addis, Ernest H. Falconer
Arthur Marlow, San Diego	Claude E. Forkner, George R. Minot, James F. Churchill
Raymond Arthur Sands, Santa Monica	Roland Cummings, Samuel M. Alter, James F. Churchill
<b>COLORADO</b>	
Paul A. Draper, Colorado Springs	A. Lee Briskman, Gerald B. Webb, James J. Waring
William Corr Service, Colorado Springs	G. Burton Gilbert, John A. Sevier, James J. Waring
John Palmer Hilton, Denver	Wilfred S. Dennis, Glaister H. Ashley, James J. Waring
<b>CONNECTICUT</b>	
Walter Ralph Steiner, Hartford	George Blumer, John A. Wentworth, Francis G. Blake
<b>DISTRICT OF COLUMBIA</b>	
John Richard Cavanagh, Washington	William M. Ballinger, Lester Neuman, Wallace M. Yater
Leslie Howson French, Washington	Oscar B. Hunter, J. B. Glenn, Wallace M. Yater
Ernest Elvin Hadley, Washington	Joseph L. Gilbert, A. C. Christie, Wallace M. Yater
Frank Stephen Horvath, Washington	James Alexander Lyon, Tomás Cajigas, Wallace M. Yater

*Candidates**Sponsors*

Earl Richard Templeton, Washington	Wm. M. Ballinger, M. W. Perry, Wallace M. Yater
George Louis Weller, Jr., Washington	W. A. Bloedorn, Walter Freeman, Wallace M. Yater

## MEDICAL CORPS, U. S. ARMY

Joseph Hall Whiteley, Coroza, C. Z.	C. R. Reynolds
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## U. S. PUBLIC HEALTH SERVICE

John William Trask, Chelsea, Mass.	Thomas Parran
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## GEORGIA

Launcelot Minor Blackford, Atlanta	Russell H. Oppenheimer, Trimble Johnson, Glenville Giddings
Thomas Sterling Claiborne, Atlanta	Roy S. Leadingham, John B. Fitts, James E. Paulin, Glenville Giddings
William Johnston Cranston, Augusta	V. P. Sydenstrieker, Eugene E. Murphey, Glenville Giddings
Hartwell Joiner, Gainesville	H. C. Sauls, John B. Fitts, Glenville Giddings
Warren Monroe Gilbert, Rome	John B. Fitts, H. C. Sauls, Glenville Giddings

## ILLINOIS

Vernon Lawrence Evans, Aurora	S. L. Gabby, J. Donald Milligan, James G. Carr
Fred Eugene Ball, Jr., Chicago	Joseph A. Capps, Arthur R. Elliott, James G. Carr
Roy R. Jamieson, Chicago	David E. Markson, Nathan S. Davis, III, James G. Carr
Henry Lenzen Schmitz, Chicago	Robert S. Berghoff, Fred M. Drennan, James G. Carr
James Bernard Berardi, Dwight	W. E. Kendall, Edward W. Hollingsworth, James G. Carr
Harry Anthony Durkin, Peoria	Henry H. Thomas, Jr., Paul Dudley White, Samuel E. Munson
Emmet Forrest Pearson, Springfield	Alfred Goldman, H. L. Alexander, David P. Barr, Samuel E. Munson

## KANSAS

William Hackney Algie, Kansas City	P. T. Bohan, Fred J. McEwen, Thomas T. Holt
Fred Ernest Angle, Kansas City	P. T. Bohan, Harold W. Palmer, Thomas T. Holt

## KENTUCKY

Max L. Garon, Louisville	Morris Flexner, J. Murray Kinsman, C. W. Dowden
Frederick George Speidel, Louisville	Oscar O. Miller, Arthur Clayton McCarty, C. W. Dowden

## MARYLAND

Raymond Hussey, Baltimore	Wm. S. Love, Jr., Thomas P. Sprunt, Henry M. Thomas, Jr.
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## MASSACHUSETTS

Egon Emil Kattwinkel, Auburndale	Dwight O'Hara, William D. Reid, William B. Breed
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*Candidates*

Maxwell Finland, Boston  
 Jerome Andrew Whitney, Long-  
 meadow  
 Milton James Quinn, Winchester

*Sponsors*

George R. Minot, Soma Weiss, William B. Breed  
 Laurence D. Chapin, George L. Steele, William B.  
 Breed  
 Frederick T. Lord, Donald S. King, William B.  
 Breed

## MICHIGAN

Bruce Hutchinson Douglas, Detroit  
 David Jacob Sandweiss, Detroit  
 Robert Jacob Schneck, Detroit  
 Joseph Francis Whinery, Grand Rapids

Wm. A. Evans, Lawrence Reynolds, Henry R.  
 Carstens  
 William H. Gordon, Laurence F. Segar, Henry R.  
 Carstens  
 Richard M. McKean, Douglas Donald, Henry R.  
 Carstens  
 Joseph B. Whinery, Burton R. Corbus, Henry R.  
 Carstens

## MINNESOTA

William Arnold Stafne, Moorhead  
 Edwin John Kepler, Rochester  
 Herman John Moersch, Rochester  
 Howard Miller Odel, Rochester  
 Edwin J. Simons, Swanville

Russell M. Wilder, Bayard T. Horton, E. L.,  
 Tuohy  
 E. V. Allen, Russell M. Wilder, E. L. Tuohy  
 E. V. Allen, F. W. Gaarde, E. L. Tuohy  
 A. R. Barnes, E. V. Allen, E. L. Tuohy  
 J. A. Myers, S. Marx White, E. L. Tuohy

## MISSOURI

Hyman I. Spector, St. Louis

Daniel L. Sexton, Alphonse McMahon, David Barr,  
 A. C. Griffith

## NEBRASKA

Joseph Daniel McCarthy, Omaha

M. C. Howard, F. W. Niehaus, Warren Thompson

## NEW JERSEY

Harold Korb Eynon, Collingswood  
 Carlyle Morris, Metuchen  
 Frederic A. Alling, Newark

G. O. Favorite, Carl C. Fischer, Clarence L. An-  
 drews  
 Frederick L. Brown, Karl Rothschild, Clarence L.  
 Andrews  
 Manfred Kraemer, Edward C. Klein, Jr., Clarence  
 L. Andrews

## NEW YORK

George Edward Anderson, Brooklyn  
 Harold Russell Merwarth, Brooklyn  
 Bernard Sternberg, Brooklyn  
 Earl Bradley Erskine, Jamaica  
 Louis Ashley Van Kleeck, Manhasset  
 Burrill B. Crohn, New York  
 John Staige Davis, Jr., New York  
 John Leonard Kantor, New York  
 Thomas Hodge McGavack, New York

Frank Bethel Cross, Tasker Howard, C. F. Tenney  
 Frank Bethel Cross, Tasker Howard, C. F. Tenney  
 David Gingold, Morris M. Banowitch, C. F. Ten-  
 ney  
 Claude E. Forkner, Goodwin A. Distler, C. F. Ten-  
 ney  
 Louis H. Bauer, Everett C. Jessup, C. F. Tenney  
 A. F. R. Andresen, T. Grier Miller, C. F. Tenney  
 Lewis F. Frissell, Walter G. Lough, C. F. Tenney  
 A. F. R. Andresen, M. D. Levy, C. F. Tenney  
 Linn J. Boyd, Milton J. Raisbeck, C. F. Tenney

*Candidates**Sponsors*

John McDowell McKinney, New York

Henry Barber Richardson, New York

Zachary Sagal, New York

Theresa Scanlan, New York

Philipp J. R. Schmahl, New York

Cornelius Horace Traeger, New York

Harry Eduarde Ungerleider, New York

S. Bernard Wortis, New York

Charles A. McKendree, Robert F. Loeb, C. F. Tenney

John A. Wentworth, Joseph H. Pratt, Eugene F. Du Bois, C. F. Tenney

Herman O. Mosenthal, Walter G. Lough, C. F. Tenney

Thomas T. Mackie, Joseph Lintz, C. F. Tenney

Linn J. Boyd, Milton J. Raisbeck, C. F. Tenney

R. Garfield Snyder, Howard F. Shattuck, C. F. Tenney

Arthur M. Master, George Bachr, C. F. Tenney

Charles A. McKendree, Robert F. Loeb, C. F. Tenney

## NORTH CAROLINA

Edward Sandling King, Wake Forest

Verne S. Caviness, Thurman Kitchin, C. H. Cocke

## OHIO

Fay Atkinson LeFevre, Cleveland

Ralph Martin Watkins, Cleveland

Russell L. Haden, C. L. Hartsock, A. B. Brower  
Chas. T. Way, H. D. Piercy, A. B. Brower

## OKLAHOMA

Samuel Charlton Shepard, Tulsa

Russell C. Pigford, E. Rankin Denny, Lea A. Riely

## OREGON

Ernest Lloyd Boylen, Portland

Blair Holcomb, Portland

Merl Lonner Margason, Portland

Merle Wayland Moore, Portland

Ralph C. Matson, Homer P. Rush, T. Homer Coffen

Homer P. Rush, John H. Fitzgibbon, T. Homer Coffen

N. W. Jones, Laurence Selling, T. Homer Coffen

Homer P. Rush, John H. Fitzgibbon, T. Homer Coffen

## PENNSYLVANIA

Paul H. Parker, Jenkintown

John Olen Woods, New Castle

Kenneth Ellmaker Appel, Philadelphia

Walter Lawrence Cahall, Philadelphia

Harold R. Keeler, Philadelphia

Charles Fay Nichols, Philadelphia

John Herbert Leyda Heintzelman,  
PittsburghH. B. Wilmer, John Eiman, Geo. Morris Piersol,  
Edward L. Bortz

Wayne W. Bissell, Eliah Kaplan, R. R. Snowden

Edward A. Strecker, David A. Cooper, Edward L. Bortz

Thomas M. McMillan, H. B. Wilmer, Edward L. Bortz

Thomas Fitz-Hugh, Jr., Edward Rose, Geo. Morris Piersol, Edward L. Bortz

Thomas Klein, Thomas M. McMillan, Edward L. Bortz

Frank A. Evans, James M. Strang, E. Bosworth  
McCreedy, R. R. Snowden

*Candidates**Sponsors*

## RHODE ISLAND

Russell Stanton Bray, Providence	Herman A. Lawson, Charles F. Gormly, Alex. M. Burgess
Henry L. C. Weyler, Providence	Charles F. Gormly, Harvey E. Wellman, Alex. M. Burgess

## SOUTH CAROLINA

Francis Eugene Zemp, Columbia	J. Heyward Gibbes, O. B. Mayer, Kenneth M. Lynch
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## TENNESSEE

Charles Roberts Thomas, Chattanooga	Leopold Shumacker, Franklin B. Bogart, J. O. Manier
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## TEXAS

William Bluford Adamson, Abilene	Erle D. Sellers, T. C. Terrell, Moise D. Levy
Wendell Heath, Paige, Brownwood	Will S. Horn, T. C. Terrell, C. T. Stone, Moise D. Levy
James John Gorman, El Paso	O. E. Egbert, C. M. Hendricks, Moise D. Levy
Julian Cox Barton, San Antonio	Lee Rice, Joe Kopecky, Moise D. Levy
Edgar Marion McPeak, San Antonio	Lee Rice, Joe Kopecky, Moise D. Levy

## VIRGINIA

James Newton Williams, Richmond	R. Finley Gayle, Jr., Dean B. Cole, J. Morrison Hutcheson
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## WASHINGTON

John Ernest Nelson, Seattle	Frederick Slyfield, Homer Wheelon, C. E. Watts
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## WEST VIRGINIA

Dudley Curtis Ashton, Beckley	J. Morrison Hutcheson, Dean B. Cole, Walter E. Vest
George Fordham, Powellton	John W. Moore, A. A. Shawkey, Walter E. Vest
Charles Belson Chapman, Welch	Albert M. Snell, A. R. Barnes, Walter E. Vest
Howard Russell Sauder, Wheeling	D. A. MacGregor, W. M. Sheppe, Walter E. Vest

## WISCONSIN

Marcos Fernan-Nunez, Milwaukee	Francis D. Murphy, W. J. Egan, Rock Sleyster
John Carl Grill, Milwaukee	Joseph Lettenberger, Francis D. Murphy, Rock Sleyster
Theodore John Pfeffer, Racine	Elmer G. Senty, A. R. Barnes, Rock Sleyster

## DOMINION OF CANADA

*Prince Edward Island*

John Wendell McKenzie, Charlottetown	A. B. Walter, R. J. Collins, H. A. Farris
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## QUEBEC

Walter de Moulpied Scriver, Montreal	Arthur T. Henderson, R. H. M. Hardisty, Charles F. Moffatt
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*Resolved*, that the following list of 10 be and herewith are elected to Fellowship in the American College of Physicians as of March 26, 1939.



*Candidates**Sponsors*

## ILLINOIS

Harold Charles Lueth, Evanston

N. S. Davis, III, Laurence E. Hines, James G. Carr

## MICHIGAN

Walter Merritt Bartlett, Benton Harbor

Russell L. Cecil, A. C. Curtis, Henry R. Carstens

Clarence E. Reyner, Detroit

Frank R. Menagh, F. Janney Smith, Henry R. Carstens

## MINNESOTA

Alexander Edward Brown, Rochester

E. V. Allen, H. C. Habein, E. L. Tuohy

## NEW YORK

Herbert Robert Edwards, New York  
Oswald Roberts Jones, New YorkJ. K. Deegan, J. Burns Amberson, Jr., C. F. Tenney  
James R. Scott, J. Burns Amberson, Jr., C. F. Tenney

Charles Aden Poindexter, New York

James G. Carr, Irving S. Wright, C. F. Tenney

## OKLAHOMA

Elmer Ray Musick, Oklahoma City

Wann Langston, John E. Heatley, Lea A. Riely

## PENNSYLVANIA

Russell Sherwood Anderson, Erie

George A. Sherman, George F. Stoney, R. R. Snowden

## VERMONT

Ellsworth Lyman Amidon, Burlington

C. H. Beecher, H. R. Ryan, Paul K. French

## ELECTIONS TO ASSOCIATESHIP

December 18, 1938

## ALABAMA

Hunt Cleveland, Anniston

Mark A. Brown, Leon Schiff, Fred Wilkerson

## ARIZONA

Orin Jocevious Farness, Tucson

Roland Davison, Charles W. Mills, Fred G. Holmes

William Roy Hewitt, Tucson

Virgil G. Presson, Samuel H. Watson, Fred G. Holmes

## ARKANSAS

Leon Earl King, Hot Springs National Park

Geo. B. Fletcher, Euclid M. Smith, Oliver C. Melson

## CALIFORNIA

Horace Bicknell Cates, Los Angeles

E. Richmond Ware, William H. Leake, James F. Churchill

Thomas B. Cunnane, Los Angeles

J. Mark Lacey, Robert W. Langley, James F. Churchill

*Candidates*

Emmett LeRoy Schield, Pomona  
 E. Minton Fetter, San Diego  
 Lyle Andrew Baker, San Francisco  
 Buford Haven Wardrip, San Jose

Roger Sherman Whitney, Colorado Springs  
 Robert William Gordon, Denver  
 Abe Ravin, Denver  
 John I. Zarit, Denver

*Sponsors*

Charles R. Castlen, E. W. Hayes, James F. Churchill  
 R. H. Sundberg, W. H. Barrow, James F. Churchill  
 William H. Leake, Chas. M. Griffith, Ernest H. Falconer  
 Earl O. G. Schmitt, Harold G. Trimble, Ernest H. Falconer

## COLORADO

James H. Brown, A. Lee Briskman, James J. Waring  
 Ward Darley, James J. Waring, Gerald B. Webb  
 James R. Arneill, R. W. Arndt, James J. Waring  
 Mathew A. Spangelberger, Harry Gauss, James J. Waring

## CONNECTICUT

Charles Tiffany Bingham, Hartford  
 Samuel Donner, Hartford  
 Maxwell Overlock Phelps, Hartford  
 Peter J. Steincrohn, Hartford  
 Robert H. Jordan, New Haven  
 Charles Arthur Breck, Wallingford

John A. Wentworth, G. Gardiner Russell, Francis G. Blake  
 O. G. Wiedman, Orin R. Witter, Francis G. Blake  
 John A. Wentworth, Orin R. Witter, Francis G. Blake  
 Orin R. Witter, O. G. Wiedman, Francis G. Blake  
 Theodore S. Evans, C. J. Bartlett, Francis G. Blake  
 J. Alfred Wilson, Cole B. Gibson, Francis G. Blake

## DISTRICT OF COLUMBIA

Theodore Judson Abernethy, Washington  
 Worth Bagley Daniels, Washington  
 Clayton Bernard Ethridge, Washington  
 Henry Anatol Monat, Washington

Walter K. Myers, Henry M. Thomas, Jr., Wallace M. Yater  
 W. A. Bloedorn, A. C. Christie, Wallace M. Yater  
 J. Winthrop Peabody, W. A. Bloedorn, Wallace M. Yater  
 George W. Calver, C. B. Conklin, Wallace M. Yater

## FLORIDA

Karl Boyles Hanson, Jacksonville  
 Franz Hahr, Stewart, Miami  
 Paul K. Jenkins, Miami Beach  
 Harold A. Ryan, Miami Beach  
 Albert W. Wallace, Miami Beach

Louie Limbaugh, Clayton E. Royce, T. Z. Cason  
 P. B. Welch, Kenneth Phillips, T. Z. Cason  
 C. F. Roche, P. B. Welch, T. Z. Cason  
 C. F. Roche, P. B. Welch, T. Z. Cason  
 C. F. Roche, P. B. Welch, T. Z. Cason

## GEORGIA

Arthur Park McGinty, Atlanta  
 Bernard Preston Wolff, Atlanta  
 Hervey Milton Cleckley, Augusta  
 Harry Taylor Harper, Jr., Augusta

Russell H. Oppenheimer, John B. Fitts, Glenville Giddings  
 Roy S. Leadingham, H. C. Sauls, Glenville Giddings  
 Edgar R. Pund, J. D. Gray, Glenville Giddings  
 V. P. Sydenstricker, J. D. Gray, Edgar R. Pund, Glenville Giddings

*Candidates*

Paul Sadler Kemp, Macon  
James Miller Byne, Jr., Waynesboro

J. Bailey Carter, Chicago  
Frank B. Queen, Chicago

Theodore Robert Van Dellen, Chicago

Willard L. Wood, Chicago  
Clarence Elliott Bell, Decatur  
Paul Spottswood Rhoads, Evanston  
John Edward McCorvie, Peoria

John McGill Porter, Concordia

Aaron Alfred Sprong, Sterling

Earl L. Mills, Wichita

William Austin Bloch, Louisville  
Adolph B. Loveman, Louisville

David S. Traub, Louisville

Oscar Blitz, New Orleans  
Donovan Clarence Browne, New Orleans  
William Howard Gillentine, New Orleans  
Isidore Leon Robbins, New Orleans  
Herbert John Schattenberg, New Orleans

Marshall Paul Byerly, Baltimore  
Henry Mathies Hensen, Baltimore  
Robert Bruce Mitchell, Jr., Baltimore  
Wendell Stanley Muncie, Baltimore  
Hugh Grigsby Whitehead, Jr., Baltimore

*Sponsors*

James A. Fountain, J. D. Gray, Glenville Giddings  
Guy G. Lunsford, Edgar R. Pund, Glenville Giddings

## ILLINOIS

A. J. Carlson, W. O. Thompson, James G. Carr  
W. Bernard Yegge, James R. Arneill, James J. Waring  
J. Roscoe Miller, Laurence E. Hines, James G. Carr  
W. O. Thompson, L. C. Gatewood, James G. Carr  
Otis O. Stanley, Cecil M. Jack, Samuel E. Munson  
Lowell D. Snorf, Arthur E. Mahle, James G. Carr  
George Parker, Orville Barbour, Samuel E. Munson

## KANSAS

William C. Menninger, Fred J. McEwen, Thomas T. Holt  
Henry N. Tihen, Harold W. Palmer, Thomas T. Holt  
Ferdinand C. Helwig, Henry N. Tihen, Thomas T. Holt

## KENTUCKY

Jno. J. Moren, Morris Flexner, C. W. Dowden  
J. Murray Kinsman, Morris Flexner, C. W. Dowden  
J. Murray Kinsman, W. E. Gardner, C. W. Dowden

## LOUISIANA

B. R. Heninger, Edgar Hull, J. E. Knighton  
Randolph Lyons, J. H. Musser, J. E. Knighton  
J. H. Musser, Philip H. Jones, J. E. Knighton  
J. H. Musser, Philip H. Jones, J. E. Knighton  
Charles W. Duval, J. H. Musser, J. E. Knighton

## MARYLAND

William S. Love, Jr., William H. Smith, Henry M. Thomas, Jr.  
Wetherbee Fort, Walter A. Baetjer, Henry M. Thomas, Jr.  
William S. Love, Jr., T. Nelson Carey, Henry M. Thomas, Jr.  
George W. Thorn, Thomas P. Sprunt, Henry M. Thomas, Jr.  
Richard France, Chas. W. Wainwright, Henry M. Thomas, Jr.

*Candidates**Sponsors*

Charles H. Conley, Jr., Buckeystown	R. W. Baer, Sydney R. Miller, Henry M. Thomas, Jr.
John Harlan Hornbaker, Hagerstown	R. S. Stauffer, Victor F. Cullen, Henry M. Thomas, Jr.
Lawrence Foss Woolley, Towson	Ross McC. Chapman, John T. King, Henry M. Thomas, Jr.

## MASSACHUSETTS

Allen Gilbert Brailey, Boston	Donald S. King, Wyman Richardson, William B. Breed
John W. Cass, Jr., Boston	Dwight L. Siscoe, J. H. Means, William B. Breed
Harold Joseph Jeghers, Boston	Chester S. Keefer, John A. Foley, William B. Breed
William Timothy O'Halloran, Boston	John A. Foley, Chester S. Keefer, William B. Breed
Richard Pratt Stetson, Boston	George R. Minot, Soma Weiss, William B. Breed
Lowrey Frederick Davenport, Brookline	Donald S. King, Henry A. Christian, William B. Breed

## MICHIGAN

Robert S. Ballmer, Ann Arbor	Arthur C. Curtis, Herman H. Riecker, Henry R. Carstens
Abraham Becker, Ann Arbor	Arthur C. Curtis, Raphael Isaacs, Henry R. Carstens
Edward Mahon Kline, Ann Arbor	Frank N. Wilson, Cyrus C. Sturgis, Henry R. Carstens
Christopher Parnall, Jr., Ann Arbor	Arthur C. Curtis, Cyrus C. Sturgis, Henry R. Carstens
Spencer Harley Wagar, Ann Arbor	Frank N. Wilson, Cyrus C. Sturgis, Henry R. Carstens
George Willard Slagle, Battle Creek	John V. Fopeano, M. A. Mortensen, Henry R. Carstens
Sidney Adler, Detroit	Hugo A. Freund, Robert C. Moehlig, Henry R. Carstens
James Ian Baltz, Detroit	Frank J. Sladen, John G. Mateer, Henry R. Carstens
C. Herbert Belknap, Detroit	George Barrie Hoops, Rollin H. Stevens, Henry R. Carstens
Benjamin I. Johnstone, Detroit	F. Janney Smith, Warren Cooksey, Henry R. Carstens
Curt Paul Schneider, Detroit	George Barrie Hoops, Rollin H. Stevens, Henry R. Carstens
Emil M. Shebesta, Detroit	Rollin H. Stevens, George Barrie Hoops, Henry R. Carstens
Lloyd Bennett Young, Detroit	George Barrie Hoops, Rollin H. Stevens, Henry R. Carstens
Benjamin Elmer Goodrich, Pleasant Ridge	F. Janney Smith, Frank R. Menagh, Henry R. Carstens
Francis James Fitzpatrick, Pontiac	Harold R. Roehm, George A. Sherman, Henry R. Carstens
Evert Waitman Meredith, Port Huron	Frank J. Sladen, F. Janney Smith, Henry R. Carstens

*Candidates**Sponsors*

## MINNESOTA

Clarence Wilber Erickson, Rochester  
 Horton Corwin Hinshaw, Rochester  
 Thomas Douglas Kendrick, Rochester  
 Alexander Robinson MacLean, Rochester  
 Arthur Seldon Mann, Rochester  
 Arthur Martin Olsen, Rochester  
 Edward Frank Rosenberg, Rochester  
 Louis Dysart Vaughn, Rochester  
 John Joseph Walsh, Rochester  
 Richard Nathaniel Washburn, Rochester  
 Donald J. Wolfram, Rochester

E. V. Allen, George B. Eusterman, E. L. Tuohy  
 E. V. Allen, A. R. Barnes, E. L. Tuohy  
 R. M. Wilder, E. V. Allen, E. L. Tuohy  
 E. V. Allen, Henry W. Woltman, E. L. Tuohy  
 Samuel F. Haines, E. V. Allen, E. L. Tuohy  
 E. V. Allen, F. A. Willius, E. L. Tuohy  
 R. M. Wilder, E. V. Allen, E. L. Tuohy  
 E. V. Allen, D. M. Berkman, E. L. Tuohy  
 Frank J. Heck, Philip S. Hench, E. L. Tuohy  
 Samuel F. Haines, Charles H. Watkins, E. L. Tuohy  
 A. R. Barnes, Austin C. Davis, E. L. Tuohy

## MISSISSIPPI

Wesley Wayne Lake, Pass Christian

Ben R. Heninger, Randolph Lyons, G. W. F. Rembert

## MISSOURI

William Byrne Brown, Columbia  
 Michael Bernreiter, Kansas City  
 Leon Bromberg, St. Louis  
 Francis B. Camp, Springfield

Elsworth S. Smith, Dan G. Stine, David Barr, A. C. Griffith  
 Sam H. Snider, Wilson A. Myers, A. C. Griffith  
 Walter M. Simpson, Harry L. Alexander, A. C. Griffith  
 G. B. Lemmon, A. L. Anderson, A. C. Griffith

## MONTANA

Charles Francis Little, Great Falls  
 Meredith Benjamin Hesdorffer, Missoula

H. W. Gregg, A. R. Foss, Louis H. Fligman  
 W. Hiemstra, A. R. Foss, Louis H. Fligman

## NEBRASKA

Willis D. Wright, Omaha

Frederick W. Niehaus, Warren Thompson, Adolph Sachs

## NEW HAMPSHIRE

Harold David Levine, Bristol  
 Joseph Dunbar Shields, Jr., Concord

Henry A. Christian, Fred E. Clow, Robert B. Kerr  
 Fred E. Clow, H. W. N. Bennett, Robert B. Kerr

## NEW JERSEY

Samuel Cohen, Jersey City  
 Arthur Milton Kraut, Jersey City  
 Charles A. Landshof, Jersey City  
 Theodore Richard Failmezger, Madison  
 Ralph Irving Alford, Montclair  
 Elizabeth Brakeley, Montclair

Thomas J. White, J. Burns Amberson, Clarence L. Andrews  
 Eugene J. Luippold, Harry J. Perlberg, Clarence L. Andrews  
 Thomas J. White, Henry T. Von Deesten, Clarence L. Andrews  
 George H. Lathrope, Irving S. Wright, Clarence L. Andrews  
 Lewis W. Brown, Edward C. Klein, Jr., Clarence L. Andrews  
 Harvey M. Ewing, Josephine B. Neal, Clarence L. Andrews

*Candidates**Sponsors*

## NEW MEXICO

Walter I. Werner, Albuquerque

J. R. Van Atta, Carl Mulky, L. S. Peters

## NEW YORK

Samuel Perkins Bailey, Brooklyn  
Benjamin M. Bernstein, BrooklynBenjamin M. Eis, Brooklyn  
Elliston Farrell, Brooklyn

Saverio Charles Franco, Brooklyn

Irving Greenfield, Brooklyn  
Alfred P. Ingegno, Brooklyn  
Leo Loewe, Brooklyn  
Emanuel Schwartz, Brooklyn  
Edmund Lester Shlevin, Brooklyn  
Lawrence Edgar Hummel, Buffalo

Richard Harry Schmit, Buffalo

Charles Wesley Martin, Far Rock-  
away

Warren Irving Titus, Glen Cove, L. I.

James Burnett Shields, Glens Falls  
David Fertig, Hartsdale  
Dwight Turney Bonham, Hempstead  
Benjamin R. Allison, Hewlett, L. I.John Leonard Byrnes, Hudson Falls  
Jacob Ernest Nadler, Jackson HeightsJohn William Pendleton Love, John-  
son CityHarold Albert Butman, Manhasset  
Edgar Willis Hainlen, Mount Morris

Harold Brandaleone, New York

Maurice Bruger, New York  
John De Paul Currence, New York  
Morris Lionel Drazin, New York  
Mack Lipkin, New York  
Leon Arthur Salmon, New YorkWilliam Andrew Somerville, New  
YorkWilliam von Stein, New York  
Edwin Wilder Gates, Niagara FallsM. M. Banowitch, Henry Joachim, C. F. Tenney  
Harry R. Litchfield, Anthony Bassler, C. F.  
TenneySimon R. Blatteis, Henry Joachim, C. F. Tenney  
Tasker Howard, J. Hamilton Crawford, C. F.  
TenneyA. F. R. Andresen, Frederick Schroeder, C. F.  
TenneyTasker Howard, Irving Gray, C. F. Tenney  
John B. D'Albora, Tasker Howard, C. F. Tenney  
Simon R. Blatteis, Henry Joachim, C. F. Tenney  
A. F. R. Andresen, Tasker Howard, C. F. Tenney  
Simon R. Blatteis, Henry Joachim, C. F. Tenney  
A. H. Aaron, Clayton W. Greene, Nelson G. Rus-  
sellRoy G. Pfozter, John M. Mesmer, Nelson G. Rus-  
sell

Louis H. Bauer, Everett C. Jessup, C. F. Tenney

Frank Bethel Cross, Everett C. Jessup, C. F.  
TenneyMorris Maslon, G. A. Chapman, C. F. Tenney  
Irving S. Wright, F. M. Jordan, C. F. Tenney  
Willard J. Davies, Roy D. Grimmer, C. F. Tenney  
Henry T. Chickering, Everett C. Jessup, C. F.  
TenneyMorris Maslon, W. H. Ordway, C. F. Tenney  
Arthur C. DeGraff, Clarence E. de la Chapelle,  
C. F. TenneyRonald L. Hamilton, C. H. Berlinghof, C. F.  
TenneyLouis H. Bauer, Willard J. Davies, C. F. Tenney  
J. K. Deegan, J. Burns Amberson, Jr., Nelson G.  
RussellElaine P. Ralli, Clarence E. de la Chapelle, C. F.  
TenneyWalter G. Lough, Milton A. Bridges, C. F. Tenney  
Walter G. Lough, Irving S. Wright, C. F. Tenney  
Carl Boettiger, Charles M. Levine, C. F. Tenney  
Walter G. Lough, Carl H. Greene, C. F. Tenney  
Charles A. McKendree, A. Wilbur Duryee, C. F.  
TenneyM. Coleman Harris, Josephine B. Neal, C. F.  
Tenney\*Arthur F. Chace, Irving S. Wright, C. F. Tenney  
Clayton W. Greene, W. R. Scott, Nelson G. Rus-  
sell

*Candidates**Sponsors*

Eugene Calvelli, Port Washington  
 Lyndon Harwood Thatcher, Poughkeepsie  
 Doran J. Stephens, Rochester  
 Daniel Milton Brumfiel, Saranac Lake

Arthur C. DeGraff, Currier McEwen, C. F. Tenney  
 Scott L. Smith, C. Knight Deyo, C. F. Tenney  
 Wm. S. McCann, Charles B. F. Gibbs, Nelson G. Russell  
 Wm. S. McCann, F. Janney Smith, Nelson G. Russell

## NORTH CAROLINA

Allyn Blythe Choate, Charlotte  
 Frank Baker Marsh, Salisbury  
 Charles Darwin Thomas, Sanatorium

Edward J. Wannamaker, T. Preston White, A. A. Barron, C. H. Cocke  
 I. H. Manning, D. Waldo Holt, C. H. Cocke  
 P. P. McCain, W. T. Rainey, C. H. Cocke

## NORTH DAKOTA

Paul Jean Breslich, Minot

Paul H. Rowe, Robert B. Radl, Julius O. Arnson

## OHIO

Karl Duren Way, Akron  
 William Parrish Garver, Cleveland  
 Mortimer L. Siegel, Cleveland  
 Carl Vernon Moore, Jr., Columbus  
 Harold Fredrick Koppe, Dayton  
 Nelson David Morris, Toledo  
 Wendell H. Bennett, Youngstown  
 John Noll, Jr., Youngstown  
 Lewis K. Reed, Youngstown  
 Charles H. Warnock, Youngstown

F. C. Potter, Joseph M. Ulrich, A. B. Brower  
 R. W. Kissane, John A. Toomey, A. B. Brower  
 Harold Feil, Chas. T. Way, A. B. Brower  
 Charles A. Doan, B. K. Wiseman, A. B. Brower  
 Walter M. Simpson, Benedict Olch, A. B. Brower  
 Carl S. Mundy, Paul M. Holmes, A. B. Brower  
 Colin R. Clark, W. H. Bunn, A. B. Brower  
 Colin R. Clark, W. H. Bunn, A. B. Brower  
 W. H. Bunn, Colin R. Clark, A. B. Brower  
 Colin R. Clark, W. H. Bunn, A. B. Brower

## OKLAHOMA

James William Finch, Hobart  
 Richard Michael Burke, Sulphur  
 Samuel Goodman, Tulsa

H. K. Speed, Arthur W. White, Lea A. Riely  
 Frank L. Jennings, E. S. Mariette, Lea A. Riely  
 Russell C. Pigford, C. J. Fishman, Lea A. Riely

## OREGON

Irvin Reginald Fox, Eugene  
 Fred Nathan Miller, Eugene

F. A. Willius, A. H. Ross, T. Homer Coffen  
 A. H. Ross, John H. Fitzgibbon, T. Homer Coffen

## PENNSYLVANIA

Alfred Winfield Dubbs, Allentown  
 Abraham Max Balter, Aspinwall  
 William Freas Confair, Benton  
 Frederick Otto Zillessen, Easton

Robert Deming Donaldson, Kane

Clara L. Davis, Lansdowne

Henry Joseph Tumen, Philadelphia  
 Ralph Charles Hoyt, Reading

Thomas Klein, Henry I. Klopp, Edward L. Bortz  
 H. M. Margolis, Milton Goldsmith, R. R. Snowden  
 William Devitt, J. Allen Jackson, Edward L. Bortz  
 John Edgar Fretz, L. G. Rowntree, Edward L. Bortz  
 George J. Kastlin, Clement R. Jones, R. R. Snowden  
 Thomas Fitz-Hugh, Jr., Frieda Baumann, Edward L. Bortz  
 H. L. Bockus, H. L. Jameson, Edward L. Bortz  
 John R. Spannuth, E. D. Funk, Edward L. Bortz

*Candidates**Sponsors*

Clair Grove Spangler, Reading

Marshall Graham, Washington

William S. Bertolet, John R. Spannuth, Edward L. Bortz

L. D. Sargent, G. W. Ramsey, E. Bosworth McCready, R. R. Snowden

## SOUTH CAROLINA

Allen Izard Josey, Columbia

J. Heyward Gibbes, O. B. Mayer, Kenneth M. Lynch

## TENNESSEE

Carl Adam Hartung, Chattanooga

Marvin Brown Corlette, Nashville

James L. Bibb, Leopold Shumacker, J. O. Manier

John B. Youmans, W. S. Leathers, J. O. Manier

## TEXAS

Max Erwin Suehs, Beaumont

Cecil Overton Patterson, Dallas

William Shelton Barcus, Fort Worth

L. T. Pruitt, V. M. Longmire, M. D. Levy

C. M. Grigsby, H. M. Winans, M. D. Levy

Will S. Horn, May Owen, C. T. Stone, M. D. Levy

William Ladelle Howell, Fort Worth

Will S. Horn, C. O. Terrell, C. T. Stone, M.D. Levy

Edward Albert Wilkerson, Houston

Daniel Davis Warren, Waco

M. D. Levy, LeRoy B. Duggan, C. T. Stone

Joe Kopecky, J. H. Musser, M. D. Levy

## VIRGINIA

William Riely Jordan, Richmond

Paul D. Camp, Dean B. Cole, J. Morrison Hutcheson

Walter Lewis Nalls, Richmond

Dean B. Cole, R. Finley Gayle, Jr., J. Morrison Hutcheson

## WEST VIRGINIA

Alfred Spates Brady, Jr., Charleston

George Francis Evans, Clarksburg

John Wm. Moore, A. A. Shawkey, Walter E. Vest

G. R. Maxwell, Edward J. Van Lier, Walter E. Vest

## WISCONSIN

Adolph Matthew Hutter, Fond du Lac

Wm. S. Middleton, Elmer L. Sevringhaus, Rock Sleyster

William Michael Jermain, Milwaukee

Joseph Lettenberger, Francis D. Murphy, Rock Sleyster

John Albert Schindler, Monroe

Wm. S. Middleton, Elmer L. Sevringhaus, Rock Sleyster

Einar Robert Daniels, Statesan

H. M. Coon, Wm. S. Middleton, Rock Sleyster

Harold Herman Fechtner, Wausau

Wm. S. Middleton, J. S. Evans, Rock Sleyster

Joseph John Furlong, Wauwatosa

Ralph A. Kinsella, Francis D. Murphy, Rock Sleyster

## PUERTO RICO

Manuel Pavia-Fernandez, San Juan

R. Rodriguez Molina, O. Costa Mandry, Ramon M. Suarez



*OBITUARY*

Henry T. Von Deesten, 268 Palisade Avenue, Jersey City, New Jersey, died September 1, 1938, after a prolonged illness terminating in cardiac failure at the age of 59.

Dr. Von Deesten was born December 9, 1879. He received his preliminary education at the Hoboken High School, Hoboken, N. J. and the Hasbrunck Institute, Jersey City, N. J. He next entered the medical department of Columbia University, New York City, from which he graduated as M.D. in 1901.

He served as intern in the Bellevue Hospital, New York, N. Y., and the St. Mary's Hospital, Hoboken, New Jersey, during 1902 and 1903, and finally took postgraduate work in the University of Berlin, Berlin, Germany, for one year before beginning the practice of medicine in his native city.

Although quite feeble during his final years, Dr. Von Deesten continued to practice as best he could and was regarded by the local profession as an outstanding consultant because of his knowledge of internal medicine.

He held many hospital appointments during his medical career as follows: Formerly, Pathologist St. Mary's Hospital, Hoboken, New Jersey; Assistant Neurologist, Polyclinic Hospital, New York City. Visiting Physician, Christ Hospital, Jersey City, N. J. and St. Mary's Hospital, Hoboken, N. J. At the time of his death, he was Consulting Physician, Christ and St. Mary's Hospitals, Hoboken, N. J. and the Bayonne Hospital and Dispensary, Bayonne, New Jersey.

He was a member of the New York Academy of Medicine, the New Jersey State Medical Society, the American Medical Association, The Jersey City Practitioners Club, Jersey City, N. J., and a Fellow of the American College of Physicians since 1920.

Dr. Von Deesten's grit and stamina to carry on after he had been stricken down with hypertensive cardiovascular disease—the bane of the medical profession—exemplifies that intangible something which makes the medical man wholly disregard himself and think only of those whose lives are entrusted to his care. It is a lesson well worth any one's while to copy and a degree of sacrifice seldom seen except in our noble profession.

The community, the profession and his bereaved family have incurred an irreparable loss.

CLARENCE L. ANDREWS, M.D., F.A.C.P.,  
Governor for New Jersey

PROGRAM  
TWENTY-THIRD ANNUAL SESSION  
AMERICAN COLLEGE OF PHYSICIANS  
NEW ORLEANS, LA.

March 27-31, 1939

GENERAL SESSIONS AND LECTURES

William J. Kerr, President

NEW ORLEANS COMMITTEE ON ARRANGEMENTS

John H. Musser, General Chairman

P. H. Jones	Robert Bernhard
Allan Eustis	John Lanford
Edgar Hull	Randolph Lyons

COMMITTEE ON CLINICS AND DEMONSTRATIONS

P. H. Jones, Chairman

O. W. Bethea	W. L. Smith
J. M. Perret	C. S. Holbrook

W. R. Wirth

COMMITTEE ON TRANSPORTATION

Edgar Hull, Chairman

L. A. Monte	G. R. Williamson
R. H. Bayley	

COMMITTEE ON ENTERTAINMENT

Robert Bernhard, Chairman

Anees Mogabgab	Ben Heninger
D. N. Silverman	Grace Goldsmith

COMMITTEE ON AUDITORIUM

Allan Eustis, Chairman

C. Tripoli	G. M. Decherd
------------	---------------

COMMITTEE ON PUBLICITY

John Lanford, Chairman

M. E. Bass	Clyde Brooks
C. J. Bloom	Maud Loeber

C. W. Duval

COMMITTEE ON ROUND TABLES

Randolph Lyons, Chairman

C. C. Bass	J. M. Bamber
J. C. Cole	

## LADIES ENTERTAINMENT COMMITTEE

Mrs. C. Grenes Cole, Chairman

## GENERAL INFORMATION

## New Orleans Headquarters

Municipal Auditorium—General Headquarters

Roosevelt Hotel—General Hotel Headquarters

Jung Hotel—Convocation Headquarters

The New Orleans Municipal Auditorium will be general headquarters for registration, exhibits, general sessions, round tables, dry clinics and special lectures.

The Roosevelt Hotel will be headquarters for Officers, Regents, Governors and members of the College; also headquarters for the Ladies Entertainment Committee and the Annual Banquet.

The Jung Hotel will be the headquarters for the Convocation and President's Reception.

List of New Orleans Hotels	Blocks from Audi- torium	Rates per day	
		Single Room with bath	Double Room with bath
ROOSEVELT HOTEL.....	7	\$3.50-6.00	\$4.50-8.00
JUNG HOTEL.....	7	3.00-4.00	5.00-8.00
De Soto Hotel.....	12	3.00-5.00	5.00-8.00
La Salle Hotel.....	5		4.00-5.00
Lafayette Hotel.....	16	2.50-3.00	3.50-5.00
Monteleone Hotel.....	8	3.00-4.00	5.00-8.00
New Orleans Hotel.....	6	3.00	4.00-6.00
St. Charles Hotel.....	11	3.00-5.00	5.00-8.00
Pontchartrain Hotel (Apartments).....	31		8.00 up

Members should make reservations directly with hotels of their choice. Mention the Convention of the American College of Physicians, for rates above quoted are, in some instances, only for this occasion.

## WHO MAY REGISTER—

- (a) All members of the American College of Physicians in good standing for 1939 (dues, if not paid previously, may be paid at the Registration Bureau).
- (b) All newly elected members.
- (c) Members of the Orleans Parish Medical Society, without registration fee, upon presentation of their 1939 membership cards.
- (d) Medical students pursuing courses at Tulane University of Louisiana School of Medicine and Louisiana State University Medical Center, without registration fee, upon presentation of matriculation cards, or other evidence of registration at these institutions; exhibits, morning lectures, dry clinics and general sessions.
- (e) House Officers of the hospitals participating in the program, without registration fee, upon presentation of proper identification; exhibits, morning lectures, dry clinics and general sessions.
- (f) Members of the Medical Corps of the Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.
- (g) Qualified physicians who may wish to attend this Session as visitors. Such physician shall pay a registration fee of \$12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

**REGISTRATION BUREAU**—Temporary Registration Bureau will be open at the Municipal Auditorium on Sunday afternoon and evening, March 26. The permanent Registration Bureau at the Auditorium will be open daily, 8:30 a.m. to 6:00 p.m., Monday to Friday, March 27–31.

**REGISTRATION BLANKS FOR ALL CLINICS, DEMONSTRATIONS AND ROUND TABLE CONFERENCES** will be sent to members of the College with the formal program. Guests will secure registration blanks at the Registration Bureau during the Session.

**BULLETIN BOARDS FOR SPECIAL ANNOUNCEMENTS** will be located in the lobby of the Roosevelt Hotel and near the Registration Bureau at the Municipal Auditorium.

**TRANSPORTATION**—On account of nationwide reductions in railroad fares, there are no convention rates any longer in effect. In many instances, however, reduced round trip tickets are in effect from certain localities. Members should consult their local ticket agents.

*Special train from the East and Midwest*—A special train will be operated from New York to New Orleans by way of Cincinnati over the Baltimore & Ohio and Louisville & Nashville Railroads, with special cars added from Pittsburgh, Detroit, Cleveland, Cincinnati and other points. A special train will be operated on the return journey from New Orleans to New York by way of the West Point route, Louisville & Nashville, Southern Railway and Pennsylvania Railroad. Special cars will also be operated by way of the Louisville & Nashville Railroad back to Cincinnati. These schedules have been arranged for the convenience of members and the best possible service is promised. Diverse routes will afford a more interesting journey. A special time-table will accompany the formal program later to be distributed to members.

## GOING JOURNEY

### Connections from New England

Saturday, March 25

	<i>E.S.T.</i>
Lv. Boston, Mass. ....	7.30 a.m.
Lv. Springfield, Mass. ....	9.25 a.m.
Lv. Hartford, Conn. ....	10.00 a.m.
Ar. New York ....	12.40 p.m.

Saturday, March 25

Lv. New York, 42nd St. Station .....	2.55 p.m.
Lv. New York, 33rd St. Station .....	2.57 p.m.
Lv. Jersey City .....	3.42 p.m.
Lv. Newark (Motor Connection) .....	3.35 p.m.
Lv. Elizabeth, N. J. ....	3.57 p.m.
Lv. West Trenton * .....	4.43 p.m.
* Special stop will be made for members to entrain.	
Lv. Philadelphia .....	5.28 p.m.
Lv. Chester, Pa. ....	5.44 p.m.
Lv. Wilmington, Del. ....	6.01 p.m.
Lv. Baltimore, Md. (Mt. Royal Sta.) .....	7.18 p.m.
Lv. Baltimore, Md. (Camden Sta.) .....	7.25 p.m.
Lv. Washington, D. C. (Union Sta.) .....	8.30 p.m.
Lv. Silver Spring, Md. ....	8.44 p.m.
Lv. Martinsburg, W. Va. ....	10.08 p.m.
Lv. Keyser, W. Va. ....	11.54 p.m.

Sunday, March 26

Lv. Chillicothe, Ohio .....	7.40 a.m.
Lv. Oakley, Ohio .....	9.29 a.m.

Ar. Cincinnati, Ohio. (Union Sta.) .....	E.S.T.
Lv. Cincinnati .....	9.50 a.m.
Lv. Louisville, Ky. ....	LOUISVILLE & NASHVILLE RR.... 10.00 a.m.
Lv. Nashville, Tenn. ....	LOUISVILLE & NASHVILLE RR "8".... 12.22 p.m.
Lv. Birmingham .....	4.45 p.m.
Lv. Birmingham .....	9.25 p.m.

## Monday, March 27

Ar. New Orleans .....	LOUISVILLE & NASHVILLE RR.... 7.55 a.m.
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## Connecting Trains

## Saturday, March 25

Lv. Pittsburgh, Pa. ....	BALTIMORE & OHIO RR.... 9.00 p.m.
Lv. Washington, Pa. ....	10.03 p.m.
Lv. Wheeling, W. Va. ....	11.20 p.m.

## Sunday, March 26

Ar. Cincinnati, Union Terminal .....	6.40 a.m.
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## Saturday, March 25

Lv. Detroit, Mich. ....	BALTIMORE & OHIO RR....*11.00 p.m.
Lv. Toledo, Ohio .....	*1.00 a.m.
* Sleeper ready at 9.30 p.m.	

## Sunday, March 26

Ar. Cincinnati (Union Sta.) .....	6.55 a.m.
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## Saturday, March 25

Lv. Cleveland, Ohio .....	BIG FOUR ROUTE....*12.15 a.m.
* Car open at 9.30 p.m.	

## Sunday, March 26

Ar. Cincinnati, Ohio, Union Terminal .....	7.00 a.m.
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## Saturday, March 25

Lv. Buffalo, N. Y. ....	NEW YORK CENTRAL RR.... 11.45 p.m.
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## Sunday, March 26

Ar. Cincinnati, Union Terminal .....	8.30 a.m.
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## Saturday, March 25

Lv. Syracuse, N. Y. ....	NEW YORK CENTRAL RR.... 8.57 p.m.
Lv. Rochester, N. Y. ....	10.30 p.m.

## Sunday, March 26

Ar. Cincinnati .....	8.30 a.m.
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## Sunday, March 26

Lv. Indianapolis, Ind. ....	PENNSYLVANIA RR.... 8.35 a.m.
Ar. Louisville, Ky. ....	11.45 a.m.

Saturday, March 25

*E.S.T.*

Lv. Chicago .....BIG FOUR ROUTE.... 11.45 p.m.

Sunday, March 26

Ar. Cincinnati, Union Terminal ..... 7.55 a.m.

*Note*

Delegates desiring to move direct to New Orleans may use ILLINOIS CENTRAL RR (Panama Limited) leaving Chicago 1.00 p.m., Sunday, March 26, arriving in New Orleans 9.00 a.m., March 27. A service charge of \$5.00 applies on this train.

Sunday, March 26

Lv. St. Louis .....ILLINOIS CENTRAL RR.... 4.45 p.m.

Monday, March 27

Ar. New Orleans, La. .... 9.00 a.m.

**RETURNING JOURNEY**

At the close of the meeting, through cars will be operated to the various cities

Friday, March 31

Lv. New Orleans, La. ....WEST POINT ROUTE.... 10.15 p.m.

Saturday, April 1

Ar. Montgomery, Ala. ....L&amp;N RR.... 7.55 a.m.

Ar. Atlanta, Ga. ....AW&amp;P RR.... 12.45 p.m.

Sunday, April 2

Ar. Washington .....SOUTHERN RY.... \*4.50 a.m.

Ar. Baltimore .....PRR.... 5.48 a.m.

Ar. Wilmington, Del. ....PRR.... 6.49 a.m.

Ar. Philadelphia, Pa. ....PRR.... 7.22 a.m.

Ar. Newark, N. J. ....PRR.... 8.58 a.m.

Ar. New York, N. Y. ....PRR.... 9.55 a.m.

The Committee on Transportation will issue full data concerning local transportation at the meeting.

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 4:45 p.m., Thursday, March 30, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the reports of the Treasurer and of the Executive Secretary, and the induction to office of the new President, Dr. O. H. Perry Pepper, Philadelphia, Pa.

BOARD AND COMMITTEE MEETINGS—The following meetings are scheduled as indicated. Special meetings will be announced and posted.

A *combined dinner* of the Board of Regents and of the Board of Governors will be given at the Roosevelt Hotel, Sunday evening, March 26, at seven o'clock.

**COMMITTEE ON CREDENTIALS**

Sunday, March 26, 9:00 a.m. ....Municipal Auditorium, Executive Secretary's Office

\* Sleeper may be occupied until 8.00 a.m.

## BOARD OF REGENTS

Municipal Auditorium, 1st Floor, First Aid Room

Sunday, March 26, 2:30 p.m.

Tuesday, March 28, 12:00 m.\*

Friday, March 31, 12:00 m.\*

## BOARD OF GOVERNORS

Municipal Auditorium, 2nd Floor, Memorial Hall (St. Peter St.)

Monday, March 27, 5:00 p.m.

Wednesday, March 29, 12:00 m.\*

## SPECIAL FEATURES

MONDAY, MARCH 27, 1939

THE ANNUAL SMOKER will be held in the Ball Room of the Roosevelt Hotel on Monday, following the evening meeting, at 10:30 o'clock. The program will consist of a series of vaudeville acts mostly by professionals. The performers of the Blue Room (Roosevelt Hotel), the best night club of the City, will put on their show, in addition to which there will be a considerable number of local performers.

The Entertainment Committee reports that the program will go from the one extreme of the rendition of negro spirituals to the other extreme of staging a fan dance. Light refreshments and beer will be served. Admission will be limited to those displaying the official registration badge. Fellows and Associates, local and guest physicians, and the technical exhibitors are invited to attend the Smoker as guests of the College.

WEDNESDAY, MARCH 29, 1939

CONVOCATION OF THE COLLEGE—8:30 p.m., Tulane Room, Jung Hotel. All Masters and Fellows of the College, and those to be received into Fellowship, should be present. Newly elected Fellows who have not yet been received into Fellowship are requested to assemble in the Lounge, mezzanine floor, just outside the Tulane Room, at 7:45 o'clock, preparatory to the formation of the procession. They will occupy especially reserved seats in the central section of the Tulane Room, to which they will be conducted by the Convocation Marshal promptly at 8:30 o'clock. It is suggested that all appear in evening dress.

The Convocation is open to all physicians and their families generally. A cordial invitation is also issued to such of the general public as may be interested.

The Convocation Ceremony will include an address by the President of the College, the presentation of newly elected Fellows, the award of the John Phillips Memorial Medal, the announcement of the Research Fellows of the College for 1939 and the presentation of the Annual Lecture.

The Presidential Reception, with dancing, will follow after a fifteen-minute intermission at the termination of the exercises. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.

THURSDAY, MARCH 30, 1939

THE ANNUAL BANQUET OF THE COLLEGE will be held in the Grand Ballroom of the Roosevelt Hotel on Thursday evening at eight o'clock. Dr. John H. Musser, General Chairman of the Twenty-third Annual Session of the College, will be the Toastmaster. Two interesting addresses will be delivered: Mrs. E. M. Gilmer, widely known as "Dorothy Dix," will tell about her experiences and letters during

\* Buffet luncheon served.

her long career as a newspaper columnist; Mr. Lyle Saxon, an historian of note, who has written such books as "Fabulous New Orleans," "Lafitte, the Pirate," and several others nationally known, will be the second speaker, and his subject will be announced later.

All members of the College, physicians of New Orleans and visitors attending the Session, with their families, are cordially invited. Tickets should be purchased at the registration bureau by Wednesday afternoon—price, \$4.00.

#### PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The Headquarters of the Women's Entertainment Committee will be located at the Roosevelt Hotel. While all visiting ladies are welcome to visit the Auditorium and inspect the exhibits, it is thought that a much more convenient and attractive headquarters for them is available at the Roosevelt Hotel. Each visitor will receive a program of the activities planned for their entertainment by the Women's Entertainment Committee. A secretary will be in charge to assist visitors in arranging their entertainment program. Visiting women are requested to register on arrival and make reservations for the events announced in the program. Additional literature containing information regarding theaters, restaurants and places of entertainment will be available at the registration desk.

The sole purpose of the Women's Entertainment Committee is to assist the visiting ladies in securing the greatest possible enjoyment and entertainment from their visit to New Orleans. It is hoped that as a result of the activities of this Committee, visitors will carry away with them the most pleasant memories of their stay. It would greatly facilitate the work of the Committee if each Fellow or Associate who will be attended by ladies will return the card accompanying the program as promptly as possible.

#### MONDAY, MARCH 27, 1939

*Morning:* Registration, Roosevelt Hotel.

*Afternoon:* 4:00 to 5:30 p.m. Tea at the Orleans Club.

*Evening:* Program (negro spirituals) at the Hutchinson Memorial.

#### TUESDAY, MARCH 28, 1939

*Morning:* Free for shopping, or to stroll down Royal Street to visit the antique shops.

*Afternoon:* 12:30 p.m. Luncheon and sight-seeing tour of the Vieux Carre; Ladies of the Woman's Auxiliary of the Orleans Parish Medical Society will act as guides. Tea will be served after the sight-seeing trip at the home of Mrs. Isaac I. Lemann in the French Quarter.

*Evening:* Bus ride through New Orleans and to the shores of Lake Pontchartrain, returning for coffee at the old French Market. Tickets, \$1.60.

#### WEDNESDAY, MARCH 29, 1939

*Morning:* 8:30 a.m. Bus trip to old plantation homes of Louisiana—an all-day trip, with luncheon served en route. Return to Roosevelt Hotel at 5:00 p.m. Fare, \$2.75.

*Evening:* 8:30 p.m. Convocation, President's Reception and Dance at the Jung Hotel.

#### THURSDAY, MARCH 30, 1939

*Morning:* 11:00 a.m. French Breakfast at the New Orleans Country Club (this may later be changed to a trip through the New Orleans parks, with a picnic luncheon served under the old dueling oaks in City Park).

*Afternoon:* Three-hour boat ride on the Mississippi River. Fare, \$1.50.

*Evening:* 8:00 p.m. Annual Banquet of the College, Roosevelt Hotel.



## VISIT TO LEPROSARIUM

An invitation has been extended by Dr. H. E. Hasseltine, of the U. S. Public Health Service, to visit the Public Health Service's Leprosarium at Carville, La., on Saturday, April 1. This is one of the most remarkable institutions of its kind in the world, and will well repay the time required to make this trip, which is some ninety miles above New Orleans on the Mississippi River.

Fellows who wish to make the trip to Carville should sign up at the Registration Desk. Transportation will be provided at a cost dependent upon the number who will go to Carville. If possible, members are asked to indicate their desire to visit the Leprosarium when they register, in order that Dr. Hasseltine may be notified twenty-four hours ahead of time of the number who anticipate attending the clinics and demonstrations, and probably the luncheon which will be served.

## SPECIAL FEATURES

*Points of Interest*

The following places will be of interest to visiting physicians and their wives to visit some time during the course of the Annual Session:

**THE NEW CHARITY HOSPITAL**—This structure, which will accommodate 2,400 patients, will be completed, but probably not occupied by the last of March. The hospital will represent the best in everything which has to do with hospital administration and the care of the sick.

**TULANE UNIVERSITY OF LOUISIANA MEDICAL SCHOOL**; Hutchinson Memorial and the Richardson Memorial, and the Hall of Science, will be open for visitors. The Hutchinson Memorial is only three blocks from the Roosevelt Hotel. In it may be viewed the Library containing the Matas Historical Exhibit, the exhibit of the Department of Tropical Medicine, and also the very interesting method of conducting an outpatient department primarily for the purpose of demonstrating to the students the proper office care of the sick individual.

**THE LOUISIANA STATE UNIVERSITY MEDICAL CENTER**—On the grounds of the Charity Hospital. This new and modern building contains a variety of medical exhibits, which should be of interest.

**TULANE UNIVERSITY**—In addition to the usual things that are to be found in a university, particularly to be emphasized, is the splendid Maya collection of Indian relics of pre-historic days, brought from Central America by various Tulane expeditions.

**THE FRENCH QUARTER**—Here may be seen The Cabildo, St. Louis Cathedral, Jackson Square, the Pontalba Buildings (incidentally, the first apartment houses in the United States), Le Petit Theater du Vieux Carre and the Patio where Lafitte was supposed to keep his booty.

**THE DELGADO MUSEUM**, the old dueling oaks, extensive playgrounds and other features may be viewed in the City Park.

Other outstanding interesting features of New Orleans include: the smallest shrine in the country, St. Roch's; the cemeteries with the bodies interred above ground; the Southern Yacht Club on Lake Pontchartrain; the new Municipal Airport, the largest in the country; the Levees.

## POST-CONVENTION CRUISES AND TOURS

(Consult Advertising Section and News Notes Section of this Issue)

**THE EXPOSITION AND TECHNICAL EXHIBIT** will be located on the main floor of the New Orleans Municipal Auditorium.

By official action of the Board of Regents of the College, the technical exhibits have been raised to a higher level of excellence through the elimination of all irrelevant and non-scientific entries. The rules adopted governing this Exhibit are as follows:

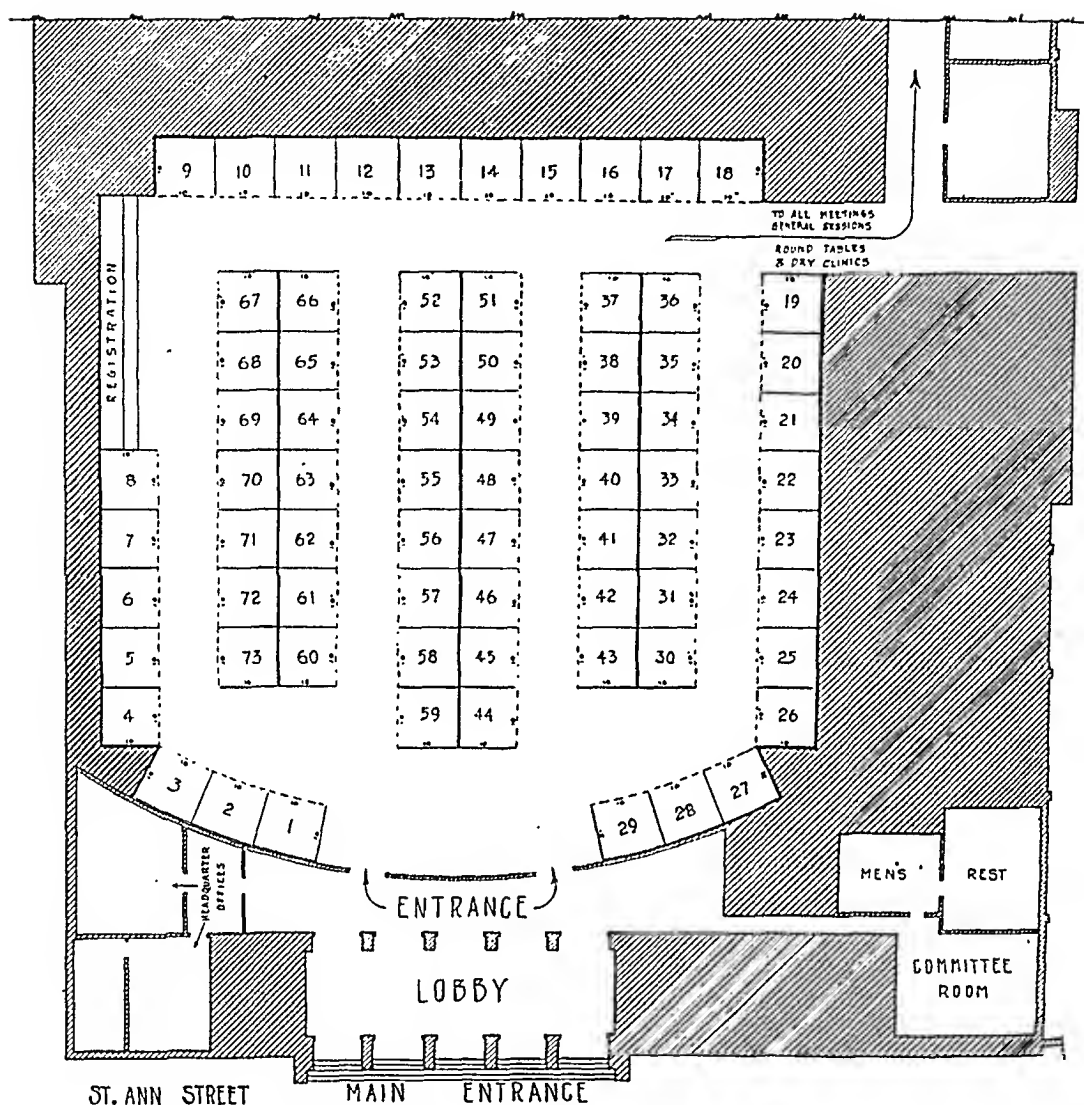
- (1) Exhibitors shall be admitted on invitation only;
- (2) The initial approved "Invitation List" shall be made up by the Committee and the Executive Secretary. Both the firm and the product must be approved. Preference shall be given to exhibits of a scientific nature, such as pharmaceuticals, equipment and medical books;
- (3) Additions to the initial approved "Invitation List" may be made by the Committee after application by firms, with the requirement that they submit complete literature concerning their products and their organization;
- (4) The "Invitation List" may be revised annually on the recommendation of the Committee.

The Committee on Exhibits has thoroughly investigated each exhibit before extending invitations. The number of exhibitors has been limited, and it is hoped that members and visiting physicians will find these exhibits more interesting and more beneficial. The exhibits will be particularly representative of the interests of Internal Medicine and its allied specialties, and will include medical literature, pharmaceutical products, apparatus and appliances, specialized physicians' furniture and many other items of special interest. Each doctor is urged to visit each of the booths, for the educational value of these exhibits adds greatly to the interesting features of the meeting. Furthermore, the exhibitors themselves solicit the courtesy of the inspection of their displays, on which they have spent much time, thought and money. Special intermissions in the general program have been arranged, providing additional time for inspection of exhibits.

### LIST OF EXHIBITORS

(Not yet complete)

	<i>Space</i>
Allison Company, W. D., Indianapolis, Ind. ....	48
Appleton-Century Company, D., New York, N. Y. ....	19
Ayerst, McKenna & Harrison (United States) Limited, Montreal, Que. ....	47
Baum Co., Inc., W. A., New York, N. Y. ....	8
Becton, Dickinson & Co., Rutherford, N. J. ....	72-73
Bilhuber-Knoll Corp., Orange, N. J. ....	30-31
Burroughs Wellcome & Co. (U. S. A.) Inc., New York, N. Y. ....	2
Cambridge Instrument Co., Inc., New York, N. Y. ....	26
Cameron Surgical Specialty Company, Chicago, Ill. ....	23-36
Collins, Inc., Warren E., Boston, Mass. ....	27
Davies, Rose & Company, Limited, Boston, Mass. ....	24
Davis Company, F. A., Philadelphia, Pa. ....	33
Devereux Schools, Inc., Berwyn, Pa. ....	56
Doak Company, The, Cleveland, Ohio ....	71
General Electric X-Ray Corporation, Chicago, Ill. ....	13-14-15
Gerber Products Company, Fremont, Mich. ....	42
Glen Springs, The, Watkins Glen, N. Y. ....	61
Gradwohl School of Laboratory Technique, St. Louis, Mo. ....	7
Heinz Co., H. J., Pittsburgh, Pa. ....	32
Hoeber, Inc., Paul B., New York, N. Y. ....	37
Jones Metabolism Equipment Co., Chicago, Ill. ....	3
Kalak Water Co., New York, N. Y. ....	9



PLAN OF TECHNICAL EXHIBIT, NEW ORLEANS MUNICIPAL AUDITORIUM

LaMotte Chemical Products Company, Baltimore, Md. ....	20
Lea & Febiger, Philadelphia, Pa. ....	59
Lederle Laboratories, Inc., New York, N. Y. ....	16-17-18
Lilly & Co., Eli, Indianapolis, Ind. ....	67-68-69
Lippincott Company, J. B., Philadelphia, Pa. ....	60
Macmillan Company, The, New York, N. Y. ....	12
Majors Co., J. A., New Orleans, La. ....	1
Mead Johnson & Company, Inc., Evansville, Ind. ....	10-11
Medical Bureau, The, Chicago, Ill. ....	43
Merck & Co. Inc., Rahway, N. J. ....	21-22
Merrell Company, The Wm. S., Cincinnati, Ohio ....	38-39
Mosby Company, The C. V., St. Louis, Mo. ....	70
Muller Laboratories, The, Baltimore, Md. ....	25
Oxford University Press, New York, N. Y. ....	28
Petrolagar Laboratories, Inc., Chicago, Ill. ....	52
Ralston Purina Co., St. Louis, Mo. ....	46

Riedel-de Haen, Inc., New York, N. Y. ....	34
Sanborn Company, Cambridge, Mass. ....	35
Saunders Company, W. B., Philadelphia, Pa. ....	1
Schering Corporation, Bloomfield, N. J. ....	66
Scientific Sugars Co., Columbus, Ind. ....	62
S. M. A. Corporation, Chicago, Ill. ....	53
Smith, Kline & French Laboratories, Philadelphia, Pa. ....	44-45
Spicer and Company, Glendale, Calif. ....	4
Squibb & Sons, E. R., New York, N. Y. ....	40-41
Stearns & Company, Frederick, Detroit, Mich. ....	29
Taylor Instrument Companies, Rochester, N. Y. ....	49-50
Westinghouse X-Ray Co., Inc., Long Island City, N. Y. ....	5-6
Winthrop Chemical Company, Inc., New York, N. Y. ....	51
Wyeth & Bro., Inc., John, Philadelphia, Pa. ....	57-58

## GENERAL SESSIONS PROGRAM

New Orleans Municipal Auditorium

## FIRST GENERAL SESSION

Monday Afternoon, March 27, 1939

Presiding Officer

John H. Musser, New Orleans, La.

p.m.

2:30 Addresses of Welcome:

Responses to Addresses of Welcome.

William J. Kerr, President of the American College of Physicians.

3:15 The Postgraduate Portion of Medical Education.

C. Sidney Burwell, Dean of the Faculty of Medicine and Research  
Professor of Clinical Medicine, Harvard University Medical School,  
Boston, Mass.

3:45 INTERMISSION.

4:15 Some Professional and Social Trends in American Medicine.

Irvin Abell, President of the American Medical Association, Louisville,  
Ky. (By invitation.)

4:45 The Limitations of Government in Medicine: The San Francisco Experience.

J. C. Geiger, Director of Public Health, City and County of San Fran-  
cisco, San Francisco, Calif.,J. P. Gray, Director of Public Welfare, City and County of San Fran-  
cisco, San Francisco, Calif. (By invitation) andA. E. Larsen, Director, Central Medical Bureau, State Relief Adminis-  
tration in San Francisco, Calif. (By invitation.)

5:15 ADJOURNMENT.

## SECOND GENERAL SESSION

Monday Evening, March 27, 1939

Presiding Officer

O. H. Perry Pepper, Philadelphia, Pa.

p.m.

8:00 The Prognosis of Bacterial Endocarditis. End Results in 129 Cases.

Joseph A. Capps, Professor of Clinical Medicine, University of Chicago;  
Attending Physician, St. Luke's Hospital; Chicago, Ill.

OUTLINE OF NEW ORLEANS SESSION

Municipal Auditorium events are indicated in bold type

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
9:00 a.m. to 12:00 m.	Morning free Registration, Exhibits, etc.	9 to 12 Hospital Clinics  10 to 12 Lectures	9 to 11 Dry Clinics  10 to 12 Round Tables	9 to 12 Hospital Clinics  10 to 12 Lectures	9 to 11 Dry Clinics  10 to 12 Round Tables
12:00 m. to 2:00 p.m.	Luncheon	Luncheon	Luncheon	Luncheon	Luncheon
2:00 p.m. to 5:00 p.m.	1st General Session	3rd General Session	4th General Session	5th General Session General Business Meeting	6th General Session
5:00 p.m. to 8:00 p.m.	Dinner	Dinner	Dinner		
8:00 p.m. to 10:00 p.m.	2nd General Session		Pre-Convocation Assembly 7:45 p.m. Convocation 8:30 p.m. Followed by President's Reception about 10:30 p.m.	ANNUAL BANQUET	
10:00 p.m. to 12:00 p.m.	Annual Smoker and Social Evening				

- 8:20 Neoprontosil (Oral) in the Treatment of Chronic Ulcerative Colitis.  
 Alex E. Brown, Associate in Medicine, Mayo Clinic, and Assistant Professor of Medicine, The Mayo Foundation; Rochester, Minn.,  
 Wallace E. Herrell, Associate in Medicine, Mayo Clinic, and Instructor in Medicine, The Mayo Foundation; Rochester, Minn., and  
 J. Arnold Barger, Associate in Medicine, Mayo Clinic, and Associate Professor of Medicine, The Mayo Foundation; Rochester, Minn.
- 8:35 The Experimental and Clinical Use of Pyridine Derivatives of Sulphanilamide in the Treatment of Bacterial Infections.  
 Perrin H. Long, Associate Professor of Medicine, Johns Hopkins University School of Medicine; Associate Physician, Johns Hopkins Hospital; Baltimore, Md. (By invitation); and  
 Eleanor A. Bliss, Fellow in Medicine, Johns Hopkins University School of Medicine, Baltimore, Md. (By invitation.)
- 8:55 Culture of Human Marrow: Studies of the Effects of Roentgen-Rays on Normal and Malignant Cells.  
 Edwin E. Osgood, Assistant Professor of Medicine, University of Oregon Medical School, Portland, Ore. (By invitation.)
- 9:10 Topic and Speaker to be announced later.
- 9:40 The Choice Between Ovarian and Pituitary Therapy for Menstrual Irregularity.  
 Elmer L. Sevringhaus, Professor of Medicine, University of Wisconsin Medical School; Associate Physician, Wisconsin General Hospital; Madison, Wis.
- 10:00 ADJOURNMENT.

10:30 o'Clock

SMOKER

Ball Room, Roosevelt Hotel

An interesting and amusing program has been arranged. Admission by registration badge.

### THIRD GENERAL SESSION

Tuesday Afternoon, March 28, 1939

Presiding Officer

William D. Stroud, Philadelphia, Pa.

p.m.

- 2:00 Recent Advances in the Understanding of the Causes of Hypertensive States.  
 Tinsley R. Harrison, Associate Professor of Internal Medicine, Vanderbilt University School of Medicine, Nashville, Tenn. (By invitation);  
 Arthur Grollman, Associate Professor of Pharmacology, Johns Hopkins University School of Medicine, Baltimore, Md. (By invitation.); and  
 John R. Williams, Jr., Research Assistant, Vanderbilt University Hospital, Nashville, Tenn. (By invitation.)
- 2:20 Gravidarteriasis.  
 Francisco deP. Miranda, Professor of Clinical Medicine, Universidad Nacional Facultad de Medicina, Mexico, D. F.

- 2:40 The Plasma Lipoids in Arteriosclerosis Obliterans.  
Nelson W. Barker, Consultant in Department of Medicine, Mayo Clinic;  
Associate Professor of Medicine, The Mayo Foundation; Rochester,  
Minn.
- 2:55 The Management of Early Essential Hypertension.  
Henry M. Thomas, Jr., Visiting Physician, Johns Hopkins Hospital,  
Baltimore, Md.
- 3:10 Five Years Experience with Mortality from Acute Coronary Occlusion in  
Philadelphia (1932-1937).  
O. F. Hedley, Passed Assistant Surgeon, U. S. Public Health Service,  
Philadelphia, Pa.
- 3:25 Roentgen Procedures Useful in Cardiac Diagnosis.  
Fred J. Hodges, Professor of Roentgenology, University of Michigan  
Medical School, Ann Arbor, Mich. (By invitation.)
- 3:45 INTERMISSION.
- 4:15 The Clinical Value of Visualization of the Chambers of the Heart, the Pul-  
monary Circulation and the Great Vessels.  
George P. Robb, Assistant in Clinical Medicine, New York University  
College of Medicine; Clinical Assistant Visiting Physician, Bellevue  
Hospital; New York, N. Y., and  
Israel Steinberg, Instructor in Medicine, New York University College  
of Medicine; Assistant Visiting Physician, Bellevue Hospital; New  
York, N. Y.
- 4:30 The Excretion Time of Quinidine from the Blood and the Heart Muscle.  
Samuel A. Weisman, Assistant Professor of Medicine, University of  
Minnesota Medical School, Minneapolis, Minn.
- 4:45 Electrocardiographic Findings Following Carotid Sinus Stimulation.  
W. Kendrick Purks, Director, Department of Internal Medicine, Vicks-  
burg Hospital, Inc., and Vicksburg Clinic; Medical Consultant,  
Mississippi State Hospital; Vicksburg, Miss.
- 5:00 Studies in the Mechanism of Cardiac Hypertrophy.  
George R. Herrmann, Professor of Clinical Medicine, Department of  
Practice of Medicine, University of Texas, Galveston, Tex.
- 5:15 ADJOURNMENT.

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#### FOURTH GENERAL SESSION

Wednesday Afternoon, March 29, 1939

Presiding Officer

David P. Barr, St. Louis, Mo.

p.m.

- 2:00 The Influence of Iron and Diet on the Blood in Pregnancy.  
Frank H. Bethell, Assistant Professor of Internal Medicine, University  
of Michigan Medical School, Ann Arbor, Mich. (By invitation.)
- 2:15 The Nutritional Significance of Nicotinic Acid.  
C. A. Elvehjem, Professor of Biochemistry, University of Wisconsin,  
Madison, Wis. (By invitation.)
- 2:35 Recent Advances in the Treatment of Pellagra.  
Tom Douglas Spies, Professor of Medicine, University of Cincinnati  
College of Medicine; Attending Physician, Cincinnati General Hos-  
pital; Cincinnati, Ohio. (By invitation.)

- 2:50 The Influence of Vitamin Deficiencies on Other Diseases.  
John B. Youmans, Associate Professor of Medicine and Director of Post-graduate Instruction, Vanderbilt University School of Medicine; Visiting Physician and Chief of Clinic of Outpatient Service, Vanderbilt University Hospital; Nashville, Tenn.
- 3:05 Clinical Studies in Acidosis and Alkalosis.  
Alexis F. Hartmann, Professor of Pediatrics, Washington University School of Medicine; Physician-in-Chief, St. Louis Children's Hospital; Pediatrician-in-Chief, St. Louis Maternity Hospital and Washington University Clinics; St. Louis, Mo. (By invitation.)
- 3:30 INTERMISSION.
- 4:00 Anaphylaxis and Allergy.  
Carl A. Dragstedt, Professor of Pharmacology, Northwestern University Medical School, Chicago, Ill. (By invitation.)
- 4:30 Epidemic Syphilis: Its Recognition and Management by the Physician.  
E. Gurney Clark, Instructor in Clinical Medicine, Vanderbilt University School of Medicine; Epidemiologist in the Syphilis Clinic and Associate Visiting Physician, Outpatient Service, Vanderbilt University Hospital; Nashville, Tenn. (By invitation.)
- 4:45 Human and Equine Encephalitis.  
James P. Leake, Medical Director, U. S. Public Health Service; In Charge of the Office of Epidemiological Studies, Division of Infectious Diseases, National Institute of Health; Washington, D. C.
- 5:05 ADJOURNMENT.

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## ANNUAL CONVOCATION

Wednesday Evening, March 29, 1939

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8:30 o'Clock

Tulane Room, Jung Hotel

All members of the profession and the general public are cordially invited. No special admission tickets will be required.

1. Address by the President of the College.  
William J. Kerr.
  2. Presentation of Newly-Elected Fellows and Recital of the Pledge.  
George Morris Piersol, Secretary-General.
  3. Presentation of John Phillips Memorial Medal for 1938-39.
  4. Announcement of Research Fellows of the College for 1939.
  5. Convocational Oration (title and speaker to be announced later).
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### *President's Reception*

The Reception and Dance will follow immediately after the program. Newly-inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.



## FIFTH GENERAL SESSION

Thursday Afternoon, March 30, 1939

Presiding Officer

Walter W. Palmer, New York, N. Y.

p.m.

- 2:00 Benign and Carcinomatous Gastric Ulcers: Their Relationship and Differentiation.

Walter L. Palmer, Associate Professor of Medicine, The School of Medicine of the Division of Biological Sciences, University of Chicago, Chicago, Ill. (By invitation.)

- 2:15 The Composition of Regenerated Liver Tissue.

B. O. Raulston, Professor of Medicine, University of Southern California School of Medicine, Los Angeles, Calif.

- 2:30 Hemolytic Jaundice: A Clinical Analysis of 28 Cases.

John C. Sharpe, Instructor in Medicine, University of Nebraska College of Medicine, Omaha, Nebr. (By invitation.)

- 2:45 A Study of the Therapeutic and Provocative Tests in Gout.

L. Maxwell Lockie, Associate in Medicine, University of Buffalo School of Medicine; Assistant Attending Physician, Outpatient Department, Buffalo General Hospital; Clinical Assistant, Inpatient Department, and Assistant Attending Physician, Outpatient Department, Children's Hospital; Buffalo, N. Y.

- 3:00 A Note on the Mechanism of Spontaneous Pneumothorax.

Louis Hamman, Associate Professor of Medicine, Johns Hopkins University School of Medicine; Visiting Physician, Johns Hopkins Hospital; Visiting Physician, Union Memorial Hospital; Baltimore, Md.

- 3:15 Specific Serotherapy and Chemotherapy of Pneumococcus Pneumonias.

Maxwell Finland, Assistant in Medicine, Harvard University Medical School; Assistant Physician, Thorndike Memorial Laboratory; Junior Visiting Physician, Boston City Hospital; Boston, Mass.

- 3:45 INTERMISSION.

- 4:15 Experimental and Clinical Observations Relating to the Management of Acute Bowel Obstructions.

Owen H. Wangenstein, Professor of Surgery, University of Minnesota Medical School; Surgeon-in-Chief, University Hospital; Minneapolis, Minn. (By invitation.)

- 4:45 ADJOURNMENT, to be followed by

## ANNUAL BUSINESS MEETING

*The Annual Business Meeting* of the College will be held immediately after the last paper. All Masters and Fellows are urged to be present. Official reports will be made by the Treasurer and the Executive Secretary; new Officers, Regents and Governors will be elected, and the President-Elect, Dr. O. H. Perry Pepper, will be inducted into office.

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Thursday Evening, 8:00 o'Clock

Grand Ballroom, Roosevelt Hotel

## THE ANNUAL BANQUET OF THE COLLEGE

(Procure Tickets at the Registration Bureau)

Consult Special Banquet Program

# SIXTH GENERAL SESSION

Friday Afternoon, March 31, 1939

Presiding Officer

Charles T. Stone, Galveston, Tex.

p.m.

- 2:00 Intersexuality or Pseudo-hermaphroditism.  
A. C. Ivy, Nathan Smith Davis Professor of Physiology and Pharmacology, Northwestern University Medical School, Chicago, Ill.
- 2:20 The Use of Dihydrotachysterol in Hypoparathyroidism.  
Homer P. Rush, Assistant Professor of Medicine, University of Oregon Medical School; Chief of Medical Service 3, Adult Hospital of the University of Oregon Medical School; Attending Physician, St. Vincent's Hospital; Attending Physician, Good Samaritan Hospital; Portland, Ore.
- 2:35 Chemical Specificity in Growth and Development.  
Stanley P. Reimann, Director of The Lankenau Hospital Research Institute; Associate Professor of Surgical Pathology, Graduate School of Medicine, University of Pennsylvania; Philadelphia, Pa. (By invitation.)
- 2:55 The Relationship Between Function and Structure of the Thyroid in the Light of Colloid Measurements.  
Eduard Uhlenhuth, Professor of Anatomy, University of Maryland School of Medicine, Baltimore, Md. (By invitation.)
- 3:25 INTERMISSION.
- 3:55 Relations Between Body Weight and Dosage of Drugs.  
W. T. Dawson, Professor of Pharmacology, University of Texas School of Medicine; Pharmacologist, John Sealy Hospital; Galveston, Tex. (By invitation.)
- 4:25 Myotonia: Its Nature and Occurrence.  
Abe Ravin, Instructor in Medicine, University of Colorado School of Medicine and Hospitals, Denver, Colo. (By invitation); and  
James J. Waring, Professor of Medicine, University of Colorado School of Medicine and Hospitals, Denver, Colo.
- 4:40 Pharmacological Treatment in Schizophrenic Patients.  
S. Katzenelbogen, Director of Laboratories and Research, St. Elizabeth's Hospital, Washington, D. C.;  
Alexander Simon, Medical Officer, St. Elizabeth's Hospital, Washington, D. C. (By invitation);  
Anna R. Coyne, Assistant Medical Officer, St. Elizabeth's Hospital, Washington, D. C. (By invitation); and  
Charles E. Vigue, Junior Medical Officer, St. Elizabeth's Hospital, Washington, D. C. (By invitation.)
- 5:00 ADJOURNMENT.

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## PROGRAM OF MORNING LECTURES

New Orleans Municipal Auditorium

This course of Lectures has become a regular feature of the program. It is presented as an elective, in place of hospital clinics. The Lectures will not conflict with the General Sessions or with the Round Table Conferences. The Lectures are

scheduled only for Tuesday and Thursday mornings, from 10:00 a.m. to 12:00 m. in the main meeting room of the Auditorium.

The Lectures will be open to all members and guests of the College. Admission by regular registration badge.

Tuesday Morning, March 28, 1939

Presiding Officer

Henry M. Thomas, Jr., Baltimore, Md.

a.m.

- 10:00 A Study of Experimental Virus Infections in the Chick Embryo.  
Ernest W. Goodpasture, Professor of Pathology, Vanderbilt University School of Medicine; Pathologist-in-Chief, Vanderbilt University Hospital; Nashville, Tenn. (By invitation.)
- 10:30 Epidemic Influenza: Studies in Clinical Epidemiology.  
Thomas Francis, Jr., Professor of Bacteriology and Director of Laboratories, New York University College of Medicine; Assistant Visiting Physician, Willard Parker Hospital; Visiting Physician on Third (New York University) Medical Division, Bellevue Hospital; New York, N. Y. (By invitation.)
- 11:00 A Study of the Nature of Bacteremia in Experimental Pneumonia.  
O. H. Robertson, Professor of Medicine, The School of Medicine of the Division of Biological Sciences, University of Chicago, Chicago, Ill. (By invitation);  
Morton Hamburger, Jr., Research Assistant, Department of Medicine, The School of Medicine of the Division of Biological Sciences, University of Chicago, Chicago, Ill. (By invitation); and  
Lucien A. Gregg, Research Assistant, Department of Medicine, The School of Medicine of the Division of Biological Sciences, University of Chicago, Chicago, Ill. (By invitation.)
- 11:30 Colored Motion Pictures of the Acute Exanthems.  
Harry A. Towsley, Instructor, Department of Pediatrics and Infectious Diseases, University of Michigan Medical School, Ann Arbor, Mich. (By invitation.)
- 12:00 ADJOURNMENT.

Thursday Morning, March 30, 1939

Presiding Officer

William B. Breed, Boston, Mass.

a.m.

- 10:00 Suggested Revisions of Medical Pharmacology.  
Paul D. Lamson, Professor of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tenn. (By invitation.)
- 10:30 Living with the Weather.  
F. M. Pottenger, Clinical Professor of Medicine, University of Southern California School of Medicine; Medical Director, The Pottenger Sanatorium and Clinic for Diseases of the Chest; Monrovia, Calif.
- 11:00 An Unwritten Chapter in the Physiology of Aging.  
A. J. Carlson, Professor of Physiology, University of Chicago, Chicago, Ill.

11:30 Newer Insulins.

Elliott P. Joslin, Medical Director, George F. Baker Clinic, New England Deaconess Hospital; Clinical Professor Emeritus, Harvard University Medical School; Boston, Mass.

12:00 ADJOURNMENT.

## ROUND TABLE CONFERENCES

The Round Tables will be held Wednesday and Friday mornings, from 10:00 a.m. to 12:00 m. They will be conducted by outstanding authorities on the subjects assigned. There will be no conflict between the Round Tables and the program of Special Lectures and General Sessions. They will, however, somewhat overlap the program of Dry Clinics, and are offered partially as an elective for the Dry Clinics between 10:00 and 11:00 o'clock on these two days. However, it will be possible for members to attend the program of Dry Clinics from 9:00 a.m. to 10:00 a.m. and attend the Round Tables from 10:00 a.m. to 12:00 m.; or it will be possible for members to attend the full program of Dry Clinics and elect Round Tables from 11:00 a.m. to 12:00 m. on these days.

The outline of Round Table Conferences and the leaders follows. The hours and room designations at the Municipal Auditorium will appear in the formal program:

CARDIOLOGY .....	Fred M. Smith, Iowa City, Iowa.
NUTRITION .....	James S. McLester, Birmingham, Ala.
NEPHRITIS .....	Wm. S. McCann, Rochester, N. Y.
BLOOD .....	R. R. Kracke, Emory University, Ga.
X-RAY .....	B. L. Kirklin, Rochester, Minn.
SULPHANILAMIDE, BACTERIAL CHEMOTHERAPY ....	P. H. Long, Baltimore, Md.
GASTRO-ENTEROLOGY .....	Lay Martin, Baltimore, Md.
PNEUMONIA .....	H. A. Reimann, Philadelphia, Pa.
SURGERY .....	Irvin Abell, Louisville, Ky.
DIABETES (Metabolic Diseases) ..	Elliott P. Joslin, Boston, Mass.
PEDIATRICS .....	A. F. Hartman, St. Louis, Mo.
ENDOCRINOLOGY .....	Elmer L. Sevringhaus, Madison, Wis.
PHYSIOLOGY .....	Carl A. Dragstedt, Chicago, Ill.
PSYCHO-SOMATIC MEDICINE ..	W. R. Houston, Austin, Tex.
PARASITOLOGY .....	E. C. Faust, New Orleans, La.

## PROGRAM OF SPECIAL CLINICS AND DEMONSTRATIONS

Practical Hospital Clinics and Demonstrations will be held from 9:00 a.m. to 12:00 m., Tuesday and Thursday mornings (March 28 and 30), instead of each of four mornings as the custom has been heretofore at the Annual Sessions of the College. However, programs of Dry Clinics will be conducted in the main meeting hall of the Municipal Auditorium from 9:00 a.m. to 11:00 a.m. on Wednesday and Friday mornings, thus supplementing the program of Hospital Clinics and Demonstrations.

Most of the Clinics and Special Demonstrations ("A," "B," "C") will be given at the Charity Hospital by the Tulane and Louisiana State University Medical School faculties. There will be three clinics and demonstrations carried on at this place. In addition to local men, a few out-of-town visitors will participate, such as Dr. Hugh Morgan, Nashville, Tenn.; Dr. Charles H. Cocke, Asheville, N. C.; Dr. James S.

McLester, Birmingham, Ala.; Dr. Samuel F. Haines, Rochester, Minn.; Dr. James E. Paullin, Atlanta, Ga. One of the features at the Charity Hospital clinics will be a daily clinico-pathologic conference which Dr. Joseph R. D'Aunoy, the Pathologist and Professor of Pathology, will conduct with some visiting clinician.

The Tulane University Clinic "D" will include not only the exhibition of patients, but also the demonstration of research work that is being conducted by the School. Clinic "E" will be held at Touro Infirmary, and will include demonstrations and clinics by members of the staff of this notable institution, together with a certain number of invited guests, including Dr. A. A. Herold, of Shreveport; Dr. Seale Harris, of Birmingham; Dr. Reginald Fitz, of Boston; Dr. R. H. Kampmeier, of Nashville; and Dr. Irving Gray, of Brooklyn. Clinic "F" will be held at the Baptist Hospital, where Dr. L. F. Bishop, Jr., of New York, will be one of the guest speakers. Clinic "G" will be held at Hotel Dieu, where Dr. F. W. Willius, of the Mayo Clinic, will be the out-of-town visitor. Clinic "H" will take place at the U. S. Marine Hospital, where, in addition to distinguished members of the U. S. Public Health Service, there will be invited to participate Dr. N. W. Barker, of the Mayo Clinic, and Dr. Walter M. Simpson, of Dayton, Ohio.

Demonstrations will be held in the Hutchinson Clinic for a small group of men on Tuesday and Thursday mornings. These will include research work and demonstration of special methods applicable to clinical medicine.

Admission will be by ticket only, otherwise crowding of the clinics and wards will interfere with effective demonstration of cases. To all members of the College registration blanks for the clinics and demonstrations will be distributed with the formal program. These registration blanks should be filled out and returned to the Executive Secretary of the College, who will select the proper tickets and hold them for members at the Registration Bureau at New Orleans. Reservations by mail cannot be made after March 20, but they may be made in person at the Registration Bureau on the evening preceding any clinic day. Guests will kindly register for clinics at the Registration Bureau upon arrival at New Orleans.

## NEW ORLEANS—WHERE WE MEET

THE history of New Orleans is not only a chronicle of material advancement, it is also a record of the progress of medical and surgical heroes. It is a saga of a titanic warfare fought by feeling individuals interested in human welfare and of employment of the implements of science for expediency's sake.

New Orleans is famed for the beauty of its women, for its chefs, its foibles and failures, and most of all, for the unbounded hospitality of its Mediterranean civilization. There are few, however, who are familiar with the gigantic combat waged by its medical men through the centuries which has lifted a struggling community out of a miasmatic swamp and made it one of the great ports of the world.

One must be reminded that the city has been visited by thirty-nine yellow fever epidemics. One of these claimed two-thirds of the city's residents. For generations its cobble stone streets rumbled with the clatter of dead wagons. Without the aid of telegraphic communication the world was never acquainted with the fact that it suffered two fires both equalling in magnitude the Chicago conflagration. The raging Mississippi has swept away its homes on countless occasions. Its people have been visited by the bubonic plague and a hundred other kindred diseases of a semi-tropic land. It has suffered famine and the ravages of war and has been occupied by invaders from its own and foreign shores. Ten flags have been raised over its surrounding dank marshes and broad fields of sugar cane.

The city's giant skyscrapers of today, its pumps which keep a community located 13 feet below sea level a healthy place in which to live, its tremendous levees holding back the mighty Mississippi are not only measures of the engineering skill or foresight of pioneers but are also monuments to its intrepid men of medicine, unheralded and unsung, who have aided in making it the metropolis of the Southern Empire.

New Orleans was founded in 1718 by Jean Baptiste Le Moyne, Sieur de Bienville, one of the greatest French colonizers. He chose the site of the town, which he hoped would eventually become capitol of the vast colony of Louisiana, on a slightly higher level of ground nestling in a great sweeping curve of the Mississippi river a little more than a hundred miles from its mouth.

Because French ministers were unable to visualize the possibilities of the site, and refused to coöperate with Bienville in developing it, the first few years of the city were not very promising. Father Charlevoix, one of the first visitors to the struggling settlement, wrote in 1722 that it consisted of a hundred barracks, a large wooden storehouse, a few tents and two or three houses, which, he observed, "would be no ornament to a village of France."

In that same year, however, Bienville, backed by Adrian de Pauger, finally succeeded in obtaining funds. From this date the city's rise began.

De Pauger, who was assistant to Le Blond de la Tour, Royal Engineer, drew up the plans for the city according to the French style. It was built within a wall, protected on three sides by a moat and on the fourth by the Mississippi river.

De Pauger marked out a square around which important public buildings of the new community were to be located and from which the city was to build out. The square was called the Place D'Armes. In 1849 its name was changed to Jackson Square in honor of the hero of the Battle of New Orleans.

The beginnings of New Orleans are still to be found in an area which the city has long since outgrown and which is known as the French Quarter, Old Quarter or Vieux Carré.

This French Quarter, the most famous single thing about New Orleans from the visitor's point of view, is very much the same now in appearance as it was towards the end of the French and Spanish dominations in the late seventeen hundreds. It is in fact a veritable treasury of historic lore—romantic and picturesque. Its exquisite wrought-iron railings, straight narrow streets, quaint architecture, fan windows and charming patios or courtyards are a never-ending source of fascination.

Recorded medical history in New Orleans begins as romantically as its first material advancement. More than 200 years ago it began with the death of a sailor, Jean Louis, a native of the city, who left the following document to the people of Louisiana.

"Nothing being more certain than death, and nothing more uncertain than its hour, being stricken with a dangerous bodily malady, but of sane mind, I desire to settle my affairs, explaining how my last will shall be carried out by my testamentary executor.

"I give to the poor of New Orleans, who are ashamed to beg, two hundred livres and also one hundred livres to procure clothes for the most needy orphans at my executor's pleasure.

"My debts having been paid and the above provisions having been executed, a sale shall be held of all that I own, the proceeds of which, together with the other monies I own, I bequeath to serve in perpetuity to the founding of a hospital for the sick of the city of New Orleans and to secure the things necessary for the sick."

Jean Louis' legacy totalled 10,000 livres. With this fund Bienville erected and equipped a hospital called the St. John's hospital or L'hospital de Pauvres de Charité or Charity Hospital.

This institution flourished for 40 years although there is no written record of the work of those brave doctors who administered to the victimized settlers roaming Louisiana's endless fever-infested swamps in search of John Law's Utopia, which had ended in the Mississippi Bubble debacle.

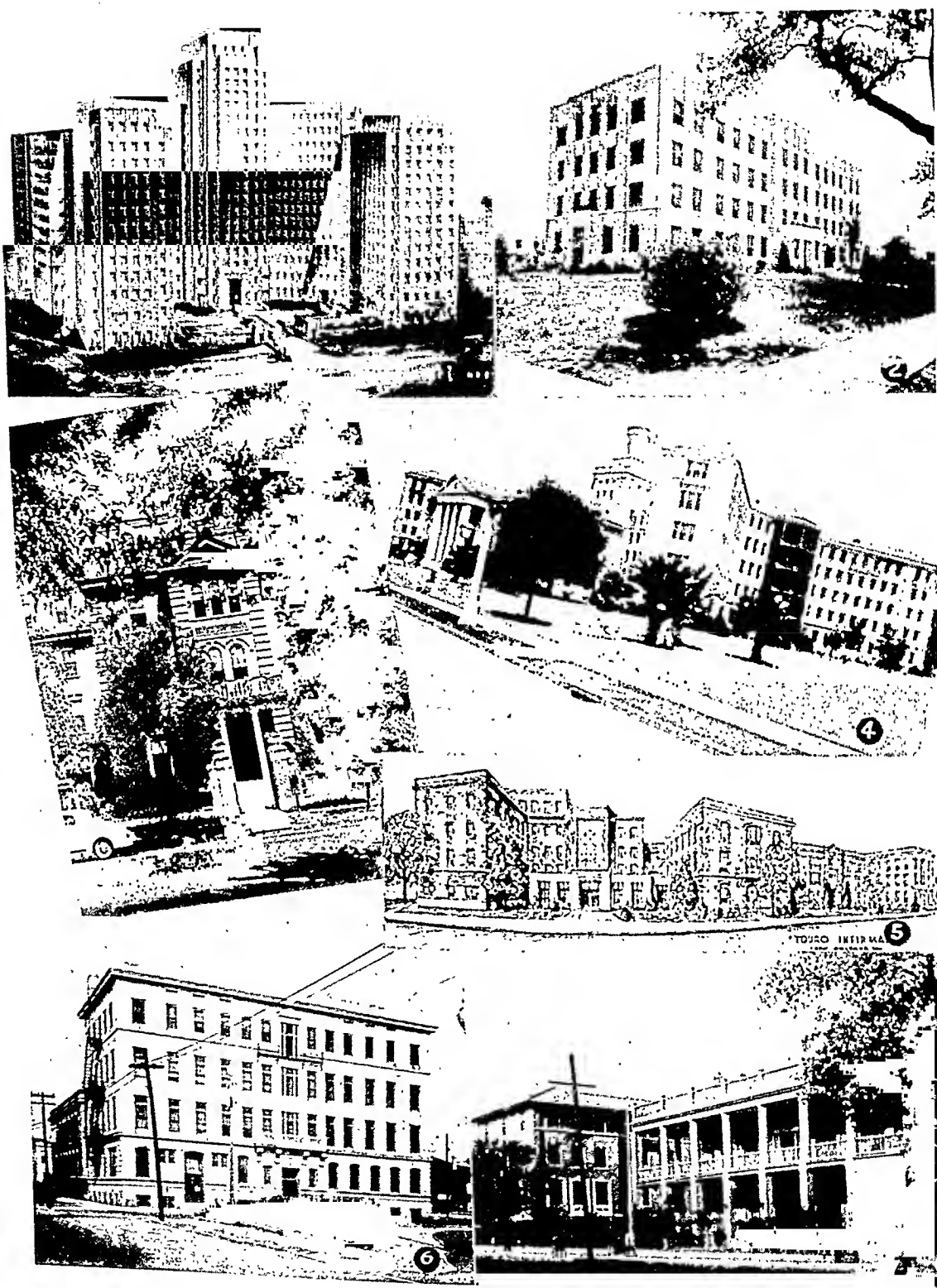


FIG. 1.

- No. 1. New Charity Hospital.
- No. 2. Flint-Goodridge Negro Hospital.
- No. 3. De Paul Sanitarium.
- No. 4. U. S. Marine Hospital.
- No. 5. Touro Infirmary.
- No. 6. Eye, Ear, Nose and Throat Hospital.
- No. 7. Mercy Hospital. Columned building in foreground is administration formerly old plantation mansion of the Soniat du Fossat plantation.



In 1779 a hurricane carried away the hospital of Jean Louis and the sick were driven into the streets. At that time Governor Don Estevan Miro wrote King Charles of Spain: "Many sick paupers are now wandering in the streets of your city in quest of shelter and aid. They are hourly exposed to perish in the very streets or die in some obscure corner."

One can imagine that at the time doctors' fees were none too high, if any at all were charged. We are told that at the time each physician carried all of his own instruments and medicines. There were but four apothecaries in the city.

Touched by the widespread misery, Don Andres Almonaster y Roxas, a grandee of old Spain and former high ranking royal army officer, donated \$140,000 for rebuilding the hospital. It took King Charles until 1782 to accept the donation and the hospital was finally built.

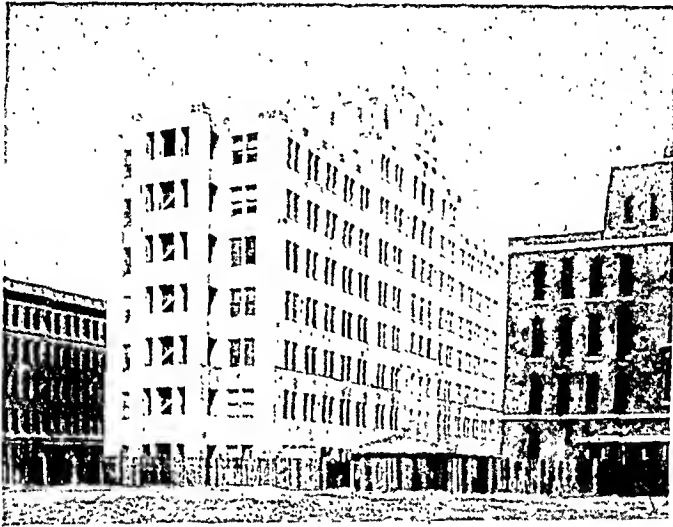


FIG. 2. Louisiana State University Medical Center. Ground in the foreground had been cleared to make room for the new \$12,000,000 Charity Hospital. The Medical center is on the grounds of Charity hospital.

On September 23, 1809, a fire leveled half of the city which had escaped a fire in 1788 and the city's only refuge for the sick was again wiped away.

Writers of the day draw a pitiful picture of the sufferings of the poor during the severe winter which followed the fire. The following year, a yellow fever epidemic swept the city. For five years the community, swarming with hordes of adventurers and mariners from all over the world, remained without a hospital. Physicians were obliged to treat the sick at hotels, in public buildings and often take them into their own residences.

In the meanwhile, Don Almonaster had died. Richest man in the colony, lawyer, statesman, contractor, architect and soldier, he was laid beneath a slab in the St. Louis Cathedral. On June 9, 1811, Micaela Almonaster, his only daughter, became the Marquese de Pontalba and, as a parting gift to

Louisiana as she left for France, gave to the state her rights as patroness of the corporation of New Orleans and the Charity Hospital.

As the eighteenth century came to a close Spain began to decay. Louisiana was again in the possession of France, and Napoleon, knowing he could not protect it from the British, sold the territory to the United States. Foreign aggression which had been holding the city down as a port of debarkation was removed and New Orleans skyrocketed to prosperity.

Craft of every description poured down the river. The population doubled, then trebled. Public buildings were erected, and the cornerstone for a greater Charity hospital was laid.

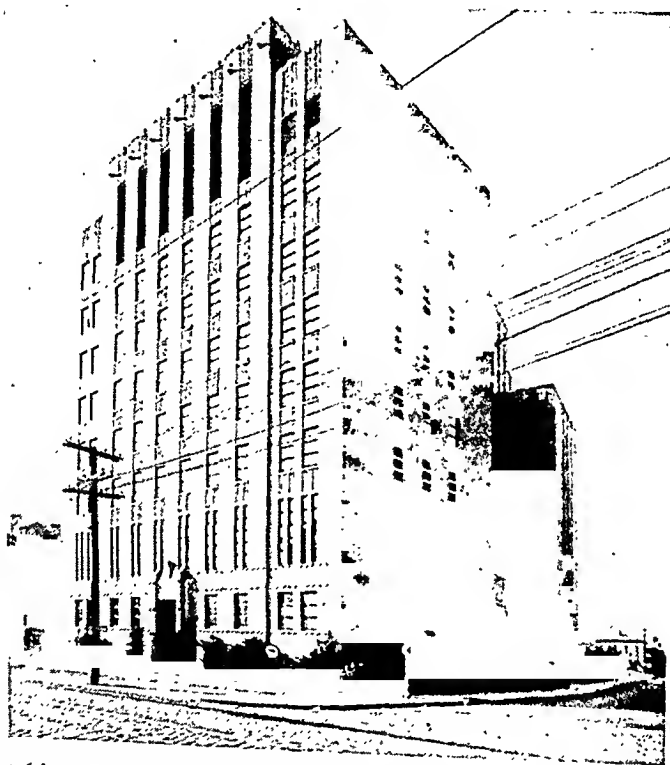
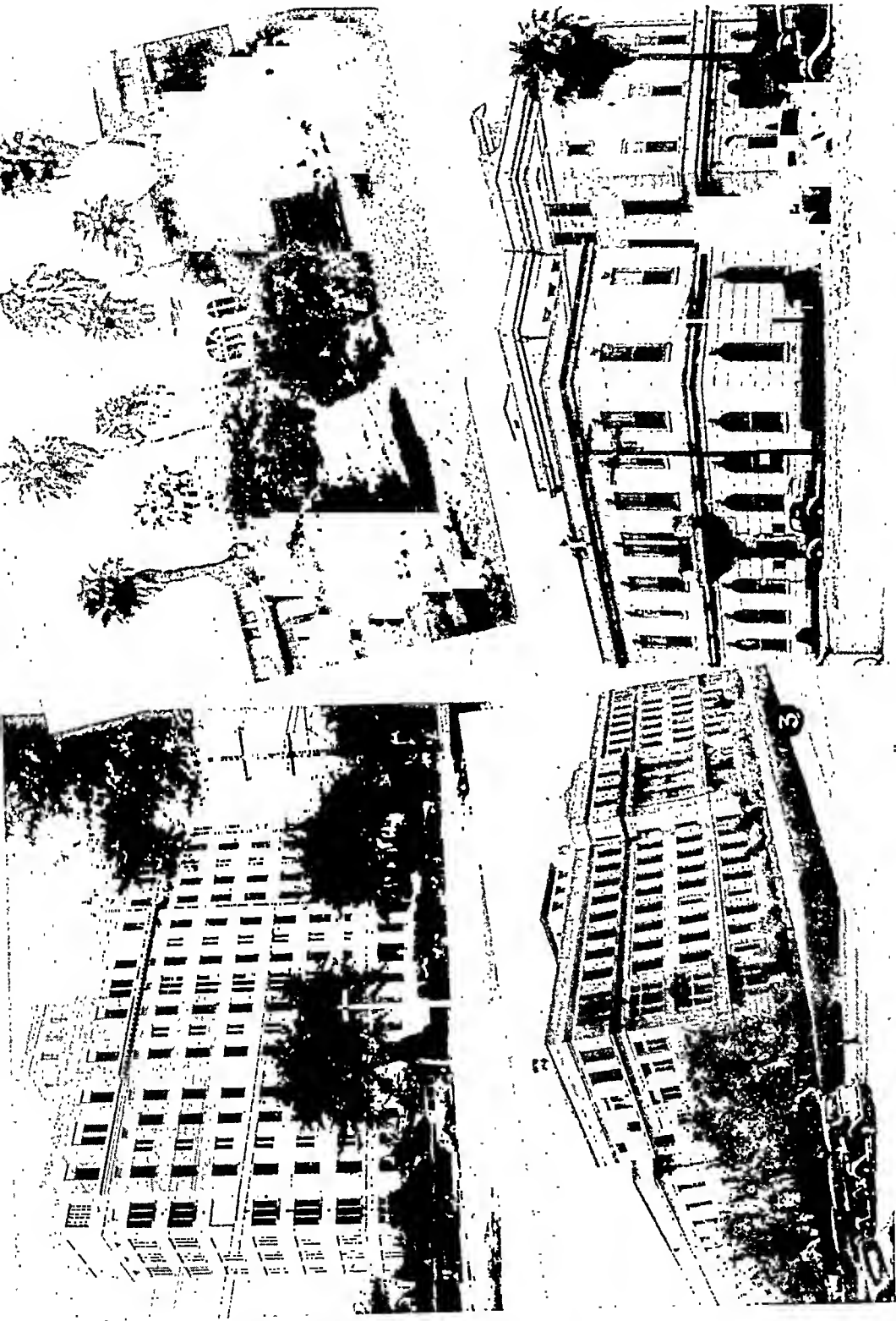


FIG. 3. The Hutchinson Memorial Building, headquarters of the School of Medicine of Tulane University. It is across the street from the new \$12,000,000 Charity Hospital.

Space does not permit the outlining of a history of those institutions which have followed Charity Hospital. Their work is evidenced by the general good health of the residents of the city. By the fact that although the city draws its water supply from the muddy Mississippi, it has the purest drinking water in the world and its death rate is low in comparison with other cities of its size.

In citing work of New Orleans physicians in the field of science, we can quote from no better source than the New Orleans City Guide, a Federal Workers Project, summarizing information on the city, which has been edited by Lyle Saxon, Louisiana's historian and writer. With permission, we quote from the guide:



Lower Left—Hotel Dieu.  
Lower Right—French Hospital.

Upper Right—Orleans Tuberculosis Hospital.  
Upper Left—Baptist Hospital.

FIG. 4.

"New Orleans has long served as a proving ground for applied science. In overcoming problems arising from the soggy nature of the subsoil, the low elevation of the city, climatic conditions favorable to malignant diseases, and the danger of Mississippi flood waters, New Orleans has made many contributions to scientific advancement.

"Noteworthy work has been done in medicine, especially in the control of yellow fever, malaria, cholera, smallpox, hookworm, and dysentery—diseases which once, because of climatic conditions, lack of adequate sewage disposal, and poor drainage, proved a scourge to the city. They are now under control and the danger of epidemics is minimized.

"Although the discovery of the causative agent of yellow fever was made elsewhere, many of the problems of practical control in large cities were solved in New Orleans by local physicians. Samuel Chopin, C. B. White, A. W. Perry, and others introduced quarantine and disinfecting methods which, though the carrier of the disease was unknown at the time, were instrumental in checking the fearful toll of yellow fever epidemics. Dr. Charles Faget contributed an indispensable diagnostic sign of yellow fever—a fall in pulse rate during the first days of the disease."

In other fields of medicine New Orleans physicians and surgeons have done much pioneer work and have made many important contributions: C. C. Bass and F. M. Johns, cultivation of the plasmodium of malarial fever; A. W. De Roaldes, establishment of the first eye, ear, nose, and throat hospital in the South; Ernest S. Lewis, pioneer work in gynecology; C. A. Luzenburg, removal of a gangrenous bowel in hernia; J. L. Riddell, invention of the binocular microscope; H. D. Schmidt, demonstration of the origin of bile ducts in intercellular spaces; A. W. Smyth, ligation of the innominate artery; Warren Stone, work on aneurysm, and resection of a rib to secure permanent drainage in empyema. Dr. Edmond Souchon developed two methods of retaining the color of muscles and organs in the preservation of anatomic dissections; the curing method using arsenic, calcium chloride, and formol; and the physical or paint method by which colorless muscles in a dissection are given permanent color. In addition to founding the Souchon Museum of Anatomy at Tulane University, he did much original work on aneurysm of the sub-clavian artery and aorta. Dr. Rudolph Matas, world-famous surgeon, has made many contributions to surgery, especially to vascular surgery, as well as a method of reducing and securing fixation of zygomatic fractures, an original method of blocking nerves in regional anesthesia, and the application of spinal subarachnoid anesthesia for surgical purposes. Valuable contributions to medical knowledge have also been made by Caine, Bruno, Jamison, Couret, Parham, Martin, and Lynch.

In dentistry, Dr. Edmund C. Kells, about thirty-five years ago, was the first to employ the roentgen-ray in his profession. A recent noteworthy accomplishment in dentistry was the method devised by Dr. S. C. Fournet and his assistant, C. S. Tuller, for stabilizing and retaining lower dentures.

The Loyola Dental School, established in 1914, is rated as a class A dental school, and is one of the best equipped institutions of its kind in the South.

In Charity Hospital New Orleans has one of the finest medical institutions in the country. Almost every physician in the city and a number practising in the neighboring parishes do part-time work at the hospital. The Medical Schools of Tulane and Louisiana State Universities train their students at the hospital and carry on much valuable research. Both medical schools rank with the best in America. The Tulane Medical School began in 1834 as the Medical College of Louisiana and merged in 1845 with the University of Louisiana, forerunner of Tulane University. In the Department of Tropical Medicine much important research is carried on in tropical diseases. The Medical Center of Louisiana State University, established in 1932, is domiciled on Charity Hospital grounds and has all the facilities of the hospital at its command. It is one of the few medical schools in the country requiring a fifth year of internship. The Flint-Goodridge Hospital is one of the South's leading hospitals for Negroes.

Principal centers of medical interest in New Orleans are:

HOTEL DIEU, 2004 Tulane Avenue, conducted by the Catholic Order of Daughters of Charity of St. Vincent de Paul, better known as the "Sisters of Charity." It is one of the oldest private institutions in Louisiana. It was founded in 1852 in a residence owned by Dr. Warren Stone and acquired its present name and site in 1858. The hospital has 175 beds, 110 nurses in training, and six resident interns in attendance.

CHARITY HOSPITAL, maintained by the state for the benefit of indigent citizens. It is at present being rebuilt and at its completion it will be one of the best equipped institutions of its kind in the United States. The buildings cover an area of three blocks fronting on Tulane Avenue. In addition to the main group of buildings, there are a number of other buildings in use, which include two structures used for repair shops, ambulance garage, and a dormitory for interns and residents.

The new main building will house 2,200 patients. To man it there will be required over 500 nurses, 190 interns and approximately 100 residents, as well as a large staff of physicians and surgeons. The building program also includes a new Nurses' Home and a number of service buildings.

Free clinics for both white and negroes are maintained as well as an accident ward open at all hours for emergency cases. Outpatients receive dental as well as medical treatment of every sort through clinics staffed by volunteer doctors. Senior students of Tulane and Louisiana State Universities are taught in these clinics.

Approximately \$1,500,000 is spent annually in the operation of the hospital. This sum is gathered largely from state appropriations, and is supplemented by numerous large gifts and the increment from trust funds left to the institution during the past 200 years.

THE CITY HOSPITAL FOR MENTAL DISEASES is housed in a three story brick building at South Broad and Perdido Streets. It was erected in 1911

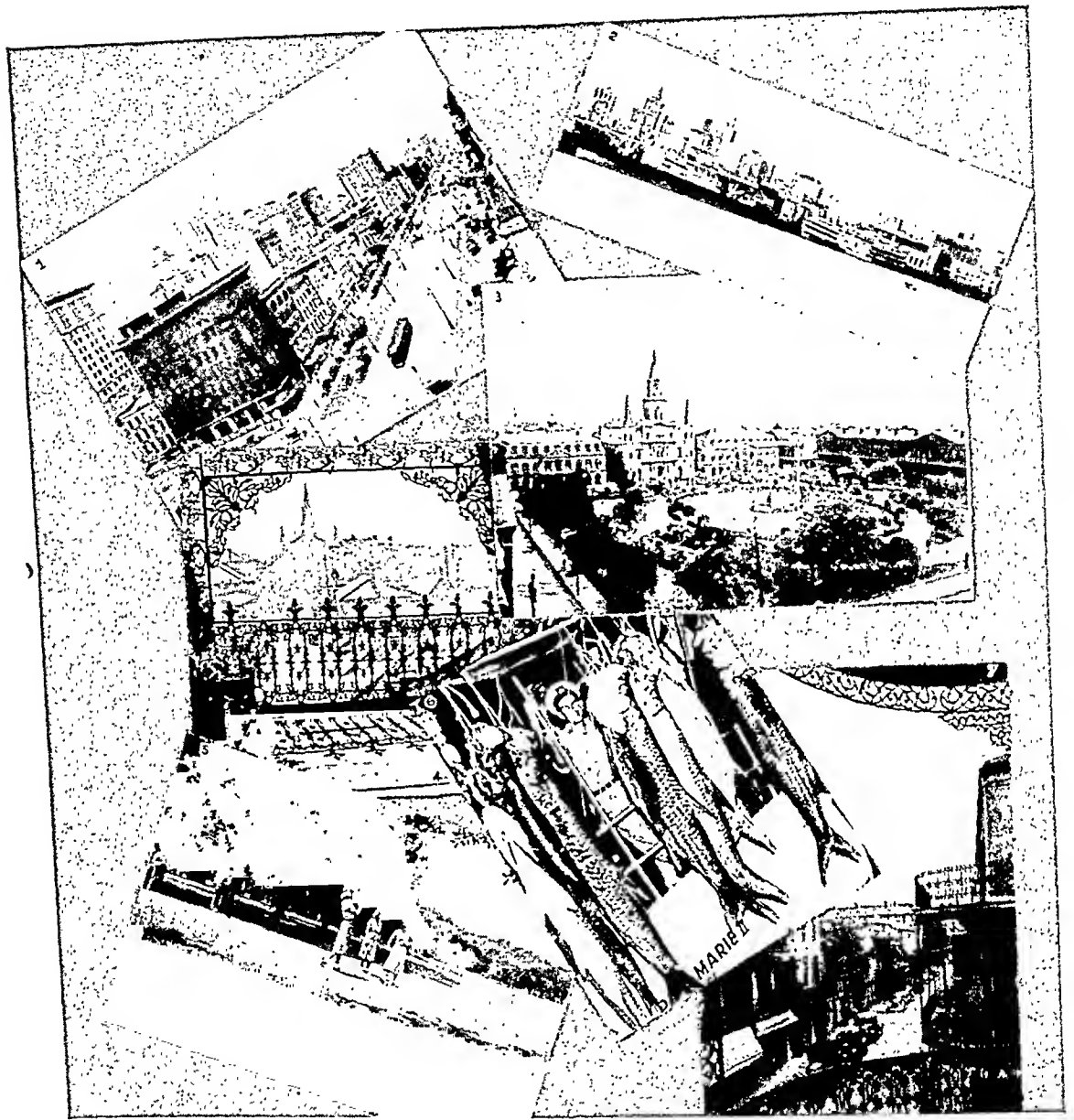


FIG. 5.

1. Historic Canal Street in New Orleans. Said to be the widest business thoroughfare in the world. The sidewalks are of pink and white terazza trimmed with brass.
2. New Orleans business district from the Mississippi.
3. The Place D'Armes or Jackson Square. Formerly the heart of New Orleans and spot where the transfer of Louisiana from France to the United States took place. On the right of the Cathedral of St. Louis, center, is the Archbishop's Palace and on the left is the Cabildo or seat of the colonial government of the territory. The long building on the right is the Pontalba Apartments, first apartment house in America.
4. Roofs of the historic Vieux Carre.
5. Audubon Park golf course, one of the city's many.
6. Fish abound all around New Orleans, in Lake Pontchartrain and in the bayous and canals.
7. The Vieux Carré is famed for its beautiful architecture and wrought iron balconies.

and has accommodations for 100 patients. Barred from hospitals, the mentally diseased were inadequately cared for. They were frequently confined to the city jails until the year 1880 when this hospital was established to house them.

LOUISIANA STATE UNIVERSITY PATHOLOGICAL MUSEUM, 1556 Tulane Avenue. Part of the LSU Medical Center contains about 1,000 mounted specimens of the most common lesions of all the anatomical systems of the body. Each specimen is accompanied by a mounted photomicrograph showing characteristic changes. A complete abstract of the clinical history, physical examination and postmortem findings in other organs in the disease process is cataloged for reference.

MUSEUM OF THE DEPARTMENT OF TROPICAL MEDICINE, at Tulane University, is located on the fifth floor of the Hutchinson Memorial Building, 1430 Tulane Avenue, regarded as one of the best in America.

Among important exhibits to be seen are those of malaria, leprosy, intestinal protozoa, plague, yellow fever, tropical diseases of the skin, venomous snakes and disease-transmitting insects and worms.

THE CHARLES EDMUND KELLS DENTAL MUSEUM AND LIBRARY, Hutchinson Memorial, Tulane University, Library second floor, Museum sixth floor. The library has 1,000 volumes dealing with dentistry. The museum contains 15 cases displaying instruments, teeth, plaster models and skulls complete.

EYE, EAR, NOSE AND THROAT HOSPITAL, 116 Elk Place, occupies two buildings. Established in 1889 by Dr. A. W. DeRoaldes, for "those too poor to pay." There are 70 beds, some are used for pay patients. Funds for operation are derived from small allotments from the State and city and from donations from citizens and payment by private patients. The staff of the hospital is composed of doctors of the city who donate their services.

TOURO INFIRMARY is a private institution under Jewish management. It is non-sectarian in its work. It operates a general clinic for both white and negroes. There are 350 beds. It was founded in the 1840's by a Jewish philanthropist Judah Touro.

MERCY HOSPITAL-SONIAT MEMORIAL HOSPITAL, 1312 Annunciation St. Founded in 1924 and operated by the Sisters of Mercy (Catholic Order). The main building is the old Soniat Plantation home, erected about 1816 on ground that was once the great Jesuit plantation where sugar cane was first introduced into America. It houses 115 beds, averages 51 nurses in training, 4 resident interns and 125 city doctors. A free clinic for white persons only is operated under auspices of the Community Chest. An average of 17,000 patients are treated free.

BAPTIST HOSPITAL, 2700 Napoleon Avenue, a nine-story brick building housing 198 beds. Constructed in 1926. There is a two-story brick building directly behind the main hospital, which is used as a nurses' home. The hospital is operated under the supervision of the Baptist Convention.

ORLEANS TUBERCULOSIS HOSPITAL, 1931 Gentilly Road, cares for indigent persons with funds provided by the Community Chest. Capacity 100 beds; admittance to the hospital must come through the Orleans Anti-Tuberculosis League located at same address.

FLINT-GOODRIDGE HOSPITAL, 2425 Louisiana Avenue. A private hospital of 100 beds operated exclusively for Negroes. It has a four-story main building facing Louisiana Avenue and behind are two one-story structures used as a nurses' home and power plant.

DE PAUL SANITARIUM, Henry Clay Avenue and Magazine Street, is a private sanitarium for mental defectives. It adjoins historic Audubon Park.

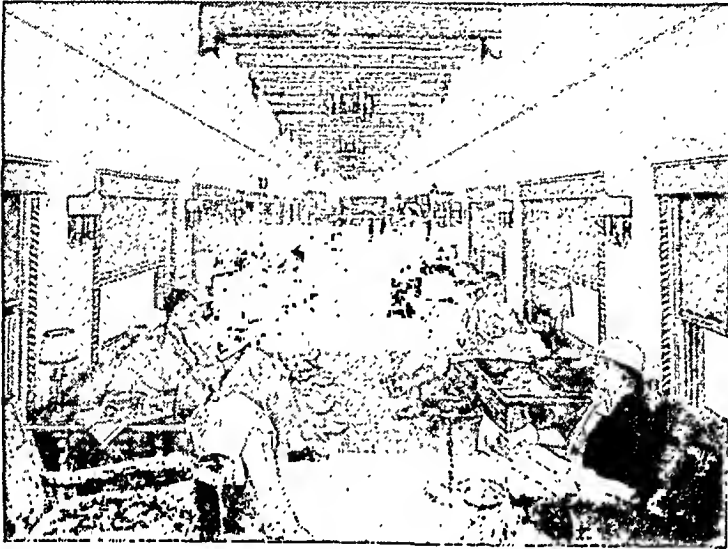
U. S. MARINE HOSPITAL, established 1830 on site of plantation of pirate Jean Lafitte at Henry Clay Avenue and State St. Operated by the U. S. Public Health Service. It averages 430 patients tended by 11 medical and dental officers, 17 medical and dental interns, 55 nurses and 7 laboratory technicians. Thirteen outside specialists in various fields of medicine and surgery are available for consultation.



## POST-CONVENTION CRUISE TO MEXICO CITY

(For itinerary, consult page 24, Advertising Section, of this Issue)

THE major Post-Convention Tour, following the New Orleans Session, will be to Mexico City. This descriptive matter supplements that appearing in the College News Notes Section, pages 900-902, of the December, 1938, issue of this Journal.



Lounge Car, Missouri Pacific.

Mexico is a decidedly foreign country and near home, yet fewer Americans have visited it than have seen Europe. Her ruins puzzle the archaeologists, there are more than hints of a one-time connection with Egypt, her scenery is lovely, her customs, language and architecture as different as you would expect in countries a thousand miles apart, her climate delightful.

The market places are always interesting whether you look or buy. Each is a riot of color and each a hubbub of commotion. On a main market day many a sleepy plaza is turned into a scene of animation, friendly and good-natured. Indians spread their wares along the ground. Oranges, tomatoes, pottery, corn and peppers mingle with gourds, with sturdy baskets, gay sarapes, toys that intrigue the adult as well as the child, puppets a few inches high, wistful, purple cows fashioned from clay and a thousand other familiar and unfamiliar articles.

Nearby is the old glass factory that has been in the same family for four generations. Here you can buy exquisite miniatures and see the famous Mexican bubble glass handblown and whirled from molten glass into finished pieces, not by artisans, but by artists.

Crafts from all parts of Mexico appear in the shops and markets of the capital. More glass from Guadalajara; lacquered boxes of olinala and

lacquered gourds; hand-tooled leather; fiber baskets with bands of black; pottery jugs and bowls with flowered decoration and many by Indians who spurn a potter's wheel.

Gold filigree jewelry, comparable to the best of the Florentine; jewelry of silver and old jade from the back streets of the capital; candlesticks, lamps and trays of hammered tin that needs no polishing; deep cream-colored pottery with strong designs in reddish brown from the mountain fastness; silver bracelets, plates and goblets, hand-hammered and etched in the tradition of ancient Toltec forebears.

Sarapes, heavy and rug-like or two-tone and light in weight; rebozos or shawls of cotton or of silk with a weave so fine they can be passed through a ring; sombreros of palmleaf fiber or with gold brocade; sashes in brilliant reds and blues; embroidery unequalled in workmanship and—oh—where shall we stop?



Market Scene.

From the steps of a modern office building one sees a sarape shrouded, sombrero-covered peon, rubbing elbows with men whose clothes bear the stamp of Broadway. Down the avenue swaggers a grandee from a distant ranch, clad in a romantic-looking charro suit of leather. Rebozo-covered Indian women sell exquisite drawn work to señoritas dressed in the height of Parisian fashions. A liveried chauffeur pilots an imported car to one side to make room for an ox-drawn cart that creaks of a century of use. On every hand are quaint pictures of native life, of whimsical activities and customs. Mexico City is rich with its own individual and characteristic brand of "local color"—an intriguing mixture of the old and the new, of the glories of Old Spain and of the new world progress.

Cuernavaca is a picturesque and delightful city with a mingling of the old and the new. Its streets are narrow, cobblestoned, and clean; some of them are flanked by fruitladen mango trees or flowering Bougainvillea. It

abounds in beautiful modern homes and is a favorite retreat of residents of Mexico City. Here was the home of the late Dwight W. Morrow. It commands a lovely view of the valley. The semi-tropical climate, cool breezes, and perpetual sunshine, even before the Spaniards conquered Mexico in the 16th century, lured nobles to Cuernavaca. Montezuma was often a visitor, Cortez built a palace there; Emperor Maximilian and Carlotta chose the Borda Gardens for their summer home; Presidents and Ambassadors have built their country mansions there.



Mexican Street Scene.

Cholula, known as "The Holy City of Anahuac" is of unfailing interest because of its large number of picturesque and quaint churches. Here is the famous convent of San Francisco where history says was celebrated the first mass in Mexico. The crowning feature of Cholula is the church on the pyramid built in the 16th century. From the stone-covered church yards if the day is clear we can see the twin peaks of Popocatepetl and Ixtaccihualt and the peak of Orizaba.

Guadalupe is the site of the most sacred shrine in Mexico, erected to Our Lady of Guadalupe on the spot where she appeared before the Indian, Juan

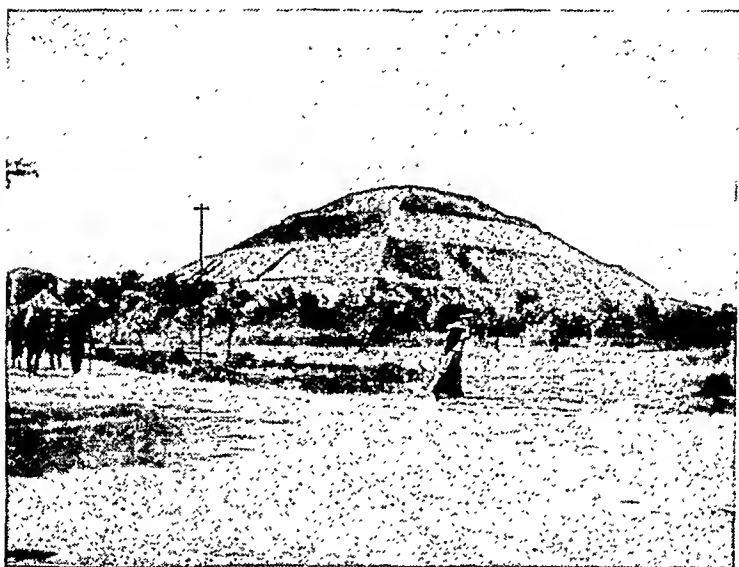
Diego, in 1531 and converted his sarape into a beautiful cloth bearing her image. This cloth is still preserved in a frame of pure gold and enclosed by a solid silver rail. The present Basilica, at the foot of Tepeyac Hill, has a beautiful interior and is the Mecca of Mexicans, visited annually by thousands of pilgrims.



Floating Gardens.

Xochimilco is a mecca because of the mystic beauty, the charm and uniqueness of the so-called "Floating Gardens." Once an Indian stronghold, it is now a new world Venice and Bangkok combined. We shall have a voyage between tiny flowered islands in a flat-bottom boat, punted by long poles in the hands of native Indians. In no place on the earth can such an experience be duplicated.

Puebla has been called "The Rome of Mexico." More than fifty interesting churches include a magnificent Cathedral unrivalled in its decorations; onyx pillars, wood-carvings, mosaics, paintings, etc., and the church of Santo Domingo which has untold riches in Churrigueresco decoration. Puebla is one of the oldest cities in Mexico and has preserved many of the architectural gems of its colonial epoch.



Pyramid of the Sun.

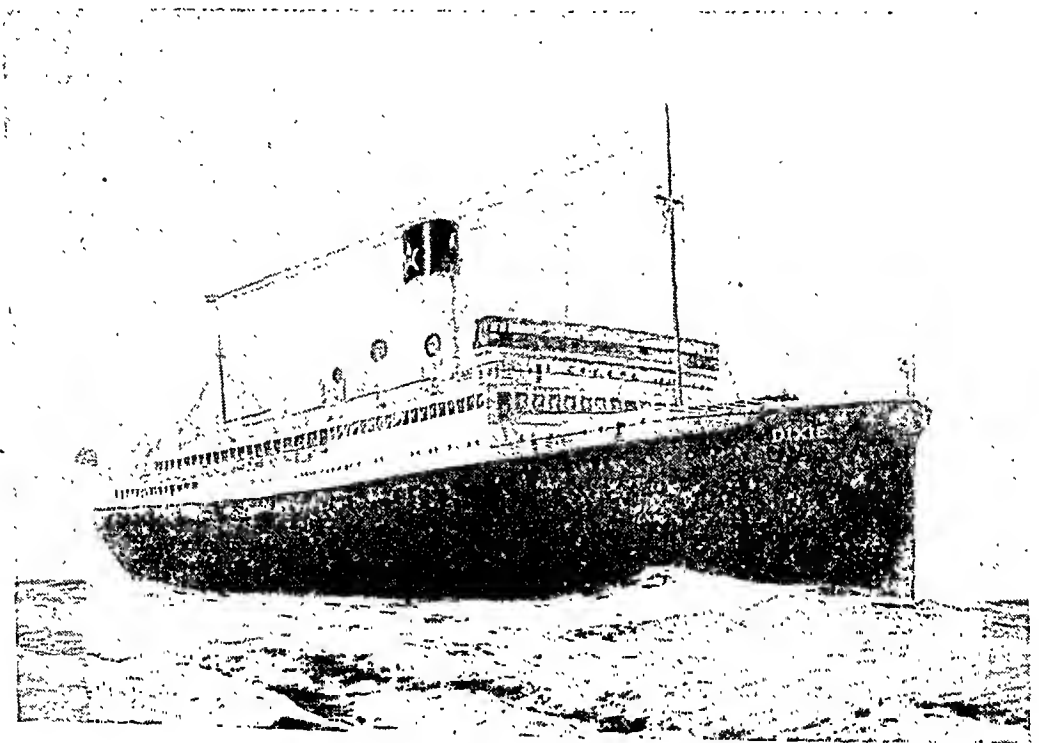
#### SAN JUAN TEOTIHUACAN AND THE PYRAMIDS

The ancient Pyramids of the Sun and the Moon at San Juan Teotihuacan are the largest artificial mounds on the continent, and the one of the Sun closely rivals the pyramids of Egypt in area and height. They mark the site of a city so ancient that there is no authentic record of when or by whom it was built. The Buried City, revealed by modern excavations, was probably built some 3000 years ago; the walls and stairways of the large rooms have polychrome decorations and are presumed to have been the palace of the ruler of the ancient inhabitants. You will be entranced with these evidences of an unknown civilization here on our own continent. You may climb the steps of the pyramid and feel like an Aztec Emperor dominating the valley at your feet. See the colored frescos on the walls of the tunnels, climb over the mounds. Who were these people, the builders? The answer is still "Who?" for though much has been written, mystery for the most part enshrouds their origin and life.

These are only a few of the interesting sights that we shall see on our motor excursion in and around the city. We have neglected Mexico from a travel angle. We, the people of the United States, have just discovered our neighbor.

## AFTER NEW ORLEANS—BACK TO NEW YORK BY WATER

WHEN the Twenty-Third Annual Session of the College at New Orleans is over, those from the East and the Northeast, or even from the Middle-west, who may not choose to accompany the special party on the Mexico City post-convention tour, but who still may desire some post-convention diversion, should consider returning from New Orleans to New York City via the *S.S. Dixie*, leaving New Orleans at 11:00 a.m., April 1, and arriving in New York City at 8:00 a.m., April 6. The cruise conductor for the College, Mr. Leon V. Arnold, 36 Washington Square West, New York City, has reserved a number of accommodations to take care of members of the College. In fact, some may wish to use the *S.S. Dixie* in both directions, and Mr. Arnold will see that proper accommodations will be provided promptly upon application to him.



THE S.S. DIXIE

On the *Dixie* many of the staterooms and suites are provided with private tub and shower baths and toilets, and all the suites and staterooms are outside, facing the sea. The passenger quarters are of American Colonial design, and public rooms include a dining salon, handsome lounge, library and music room; observation sun parlor and dance room; smoking room and modern bar; barber shop; and a commodious built-in outdoor swimming

pool. There is hot and cold running water in all the rooms, and hot and cold fresh and salt water is supplied to all baths. All the rooms have electric fans, thermos bottles for drinking water, wardrobes and full-length mirrors.

Some members will wish to extend the Convention period into a holiday period. The *Dixie* makes it possible to enjoy the good fellowship of old friends and new in either or both directions for "one hundred golden hours at sea."

On the southbound journey, after passing Sandy Hook on the *Dixie*, the attractive Jersey coast with its famous resorts is kept in view until Atlantic City is passed during the night of the first sailing day. At about six o'clock the next evening, when off Hatteras on the coast of North Carolina, the steamer's course is shaped across the Gulf Stream—that mysterious and vast ocean current that issues out of the Caribbean Sea and the Gulf of Mexico.

A change from the deep blue of the Gulf Stream to the emerald green of the open sea discloses to the voyager that only a few hours were consumed in crossing the Stream. It is entered again when the vessel is near Matanilla Reef and the Great Bahama Islands. Then, about 2:00 p.m., three days after leaving New York, Jupiter Light on the coast of Florida is sighted.

The ship's course is now lying only a few miles off shore and the Florida coast is kept in sight during the remainder of the day, affording a clear view of the Florida resorts, including Palm Beach and Miami. An interesting succession of beacon lights is strung along the coast, interspersed here and there with stretches of glittering highways, village and resort lights, that present a brilliant and fascinating spectacle as the steamer proceeds down the coast during the night.

Early the next morning Sand Key, the southernmost point in the United States and within 57 miles of the line of the Tropics, is passed. And now we see Key West in the distance. Then we pass Rebecca Shoals Light, Garden Key—on which Fort Jefferson is located—and Dry Tortugas, after which the course is shaped northwesterly across the Gulf of Mexico. The sunsets here are beautiful as vast white clouds pile up in fantastic shapes and the setting sun makes the water gleam like gold while the whole range of visibility is suffused with a purple glow. Twice is this view possible, for the transit of the Gulf includes the evening hours of two days.

South Pass, at the Delta of the Mississippi River and one of the strangest marine gateways in the world, is made at about nine o'clock on the last night. Here the river pilot is taken aboard to direct the ship up the 105 miles of the Mississippi River to the pier in New Orleans, which we reach at seven o'clock in the morning.

Northbound the route is in reverse and equally as alluring and delightful.

For all information, plan of the ship, reservations, etc., write to Mr. E. R. Loveland, Executive Secretary, the American College of Physicians, 4200 Pine St., Philadelphia, Pa., or Mr. Leon V. Arnold, 36 Washington Square West, New York City.

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## PROPHYLAXIS IN ALLERGY \*

By RICHARD A. KERN, M.D., F.A.C.P., *Philadelphia, Pa.*

WHEN an allergist, confronted with the difficult and at times hopeless problem of the patient with advanced allergic disease, traces back the story to its beginnings—the severe and perennial asthma, that a few years ago was only an occasional attack, and before that, mild nasal symptoms, untreated because they seemed so insignificant—he cannot help but think how much easier it would have been to help this patient in those earlier stages, and why was nothing done to prevent the onset and progress of his various sensitivities? Although our knowledge of the development of the allergic state is as yet defective and fragmentary, nevertheless enough information is at hand to warrant its practical application. And so some allergists in their writings (Cooke,<sup>1</sup> Rowe,<sup>2</sup> Tuft,<sup>3</sup> Vaughan,<sup>4</sup> and others) have mentioned and most allergists in their clinical practice have advised measures which they felt might prevent the onset of allergic disease. Unfortunately the possibility of prophylaxis has not been brought with sufficient insistence to the attention of internists, pediatricians, general practitioners, and others not primarily interested in allergy. As a result, prophylaxis has been least attempted in the very persons most in need of it: those not yet afflicted with clinical hypersensitiveness, or only in its milder forms. It therefore seemed worth while to present this subject to non-allergists for their earnest consideration and use.

Correct prophylaxis must be based on a knowledge of underlying causes. Here our ignorance sets major limitations. We do not know *why* people become hypersensitive and so we cannot attack the problem from this fundamental aspect. But as to *how* they become hypersensitive we have accumulated both clinical and experimental data on which to base our attempts at prevention. Let us therefore consider the factors which appear to be involved in *how* persons become allergic.

The outstanding etiologic factor in human hypersensitiveness is *heredity*. There are few diseases in which the hereditary factor is more firmly estab-

\* Presented before The American College of Physicians, New York, April 5, 1938.  
From the Division of Medicine, Allergy Section, Hospital of the University of Pennsylvania.



lished and there is none which is as common in every-day experience. That which is inherited is not a specific manifestation of allergy, such as asthma, or a sensitivity to a specific substance, for example, ragweed pollen, but the ability to become sensitized to a wide range of things in the environment far more easily than do normal persons.

To trace the hereditary factor in allergic disease is not as simple as it is in most hereditary diseases, and for several reasons: The clinical manifestations of allergy are numerous and varied, and commonly of so mild a degree as to go unrecognized as allergic. The things to which persons become hypersensitive as well as the parts of the body so sensitized are very largely a matter of chance and of the peculiarities of an individual's experiences. Clinical sensitivity in those hereditarily disposed may never occur, because the person did not encounter the proper conditioning circumstances that would bring out his hereditary defect, especially if intercurrent disease or accident killed him before the age at which he would probably have developed allergic symptoms. In taking a family history for possible allergy we must therefore be mindful to inquire about a considerable number of conditions that might be of allergic nature, and especially about the milder forms of allergic disease, such as apparently slight food or drug idiosyncrasies, trifling but persistently recurring skin rashes whenever certain things are eaten or touched, mild or severe headaches suggesting migraine, and excessive sneezing—the normal person is entitled to two or at most three consecutive sneezes: if a patient habitually sneezes six times in a row, he is in all likelihood as clearly allergic as if his presenting symptom were severe asthma. We must be prepared to encounter apparent gaps in the story of heredity, especially when a mild type of allergy has been overlooked. A corollary to the latter thought is that whenever possible the family history should be elicited through a woman member of the family, since men are woefully uninformed on these matters.

Heredity seems to be operative in the following manner. The defect appears to be passed on as a dominant characteristic according to the Mendelian law. Since those with the allergic defect are from a genetic standpoint to be considered as hybrids, it follows that, when both parents are allergic, about 75 per cent of the offspring will have the defect. If only one parent is allergic, about 35 to 40 per cent of the offspring will be potential allergics. An important point in the matter of heredity in allergy is this: the more marked the allergic background of an individual, the more marked will be the allergic defect he can inherit, and consequently the earlier in life (infancy!) will allergic symptoms develop and the more varied will they be in the course of his lifetime. While it is by no means the rule, nevertheless there is a definite tendency to find in a patient with sensitivity to inhaled substances a preponderance of inhalant allergy in the family history, whereas the patient sensitive to things ingested more commonly gives a family history of that type of allergy.<sup>5</sup> But above all, the point to be stressed is that the thing inherited is the capacity easily to be sensitized, a

capacity which the allergic carries from the cradle to the grave and which may and often does color the picture of his medical experiences throughout life.

In connection with heredity one must also consider the possibility of sensitization of the fetus in utero. This might occur either by way of passive transfer of sensitizing antibodies existing in the blood of a sensitive mother across the placental circulation, or by the similar passage into the fetus of unsplit proteins of foods which the mother has eaten. In the former instance the fetus would become sensitized to the same food to which the mother is sensitive, in the latter, to some of the foods which the mother happens to have eaten. In man as in the guinea pig the placenta has a covering only one cell thick, which renders that organ much more permeable to substances circulating in the maternal blood than is the case with the multi-layered placental membrane of most mammals. There is both experimental and clinical evidence to show that sensitization of the fetus in the guinea pig and in man may so occur, and in man this may account for the somewhat more frequent history of heredity of allergy through the mother. How important such intrauterine sensitization is in clinical allergy, we do not know. The evidence at hand tentatively suggests that it is not a major factor and that when present it has to do more with sensitivity to foods than to other substances.

What is known of that which tends to bring about sensitivity in those so disposed by heredity? Clinical experience strongly suggests the following factors:

- (1) *The ease of permeability of the involved body surface to the sensitizing substance to which it is exposed.*
- (2) *The intensity of such exposure, especially with sharply increased concentrations of the sensitizing substance.*
- (3) *The increased vulnerability of the exposed surface incident to infection or trauma involving that surface.*

It would follow, then, that the skin with its dry surface offers a fairly effective barrier to the foreign substance. This is in line with clinical experience, for sensitization takes place much less frequently by way of the skin than by way of the mucosa of the digestive or respiratory tracts. Sensitization through the skin is enhanced by moisture which both dissolves the sensitizing substance and makes the macerated skin more permeable. This may be only the increased moisture of perspiration in summer, that, for example, dissolves enough nickel out of the white gold of eye glasses or wrist watch and so accounts for the usual summer onset of such skin sensitivity to nickel. More commonly there is a more obvious exposure to moisture, as in case of the baker, the skin of whose hands becomes sensitive to the wheat protein of the dough which he kneads, or the surgeon who develops a sensitivity to the antiseptic solutions which he uses. Infections of the skin, notably when there are favorable conditions from the standpoint

of moisture, may play a part. The outstanding example is offered by the fungus infections between the toes and the consequent generalized skin sensitivity, termed dermatophytid by the dermatologists, which may arise especially in those of allergic background. Sensitization by way of the skin commonly does not progress beyond the skin to involve other parts of the body.

The mucosa of the digestive tract with its moist surface, its prolonged intimate contact with ingested substances, and its primary function as an absorbing organ, offers a much easier means of entry for the sensitizing substance. Sensitization by way of the digestive tract is therefore a very common occurrence. While in milder cases the sensitivity may possibly remain localized in more or less restricted portions of the gut tube, such sensitivity can and usually does involve any one or several of the body tissues that are capable of acting as shock organs, and so give rise to the most diverse clinical manifestations of allergy.

There are, however, at least two factors operative with regard to the digestive tract that act in a measure against sensitization by this route: cooking and digestion. Cooking commonly applies sufficient heat to alter the nature of ingested proteins so that they may neither act as sensitizing agents to the non-sensitive nor as shock doses to those already sensitized. This accounts for two well-known clinical facts: the greater frequency of sensitivity to foods eaten in the raw state, and the ability of many patients to eat with impunity a cooked food, that eaten raw would provoke symptoms. Digestion probably also in a measure protects against the absorption of undue amounts of unsplit proteins. It has, however, been well established that in this regard digestion is only a very imperfect protection, for it can be shown that tiny amounts of unaltered proteins are constantly being absorbed from the digestive tract. Nevertheless, this imperfect barrier of digestion may under circumstances be still further impaired and so be responsible for the development of sensitization. If this be true, it would in part account for the higher incidence of food sensitivity in infancy when the adequate presence of gastric free hydrochloric acid and consequent normal peptic digestion has not yet been established, and the renewed incidence of such sensitivity in late middle life when gastric anacidity again becomes more frequent. This latter association is, however, by no means constant.

The mechanical factor, stasis, may at times definitely favor the absorption of incompletely digested food, especially if the stasis be high in the gut tube, in the duodenum. Certainly there would appear to be a more than casual relation between duodenal stasis and migraine due to food allergy. Certainly the correction of duodenal stasis is commonly quite as successful in preventing the migraine as is the avoidance of a specific food.

Whether liver disease, by interfering with a possible protective function of that organ against unsplit protein absorbed in the digestive tract, may be a factor in the development of food allergy, as suggested by Urbach,<sup>6</sup> and others, while theoretically plausible, lacks confirmation.

Most vulnerable is the mucosa of the respiratory tract, with its moist surface on which the foreign substances are dissolved, its lack of any digestive mechanism that could protect it, and its contact with the foreign substances in their native, unaltered state. It is not surprising, therefore, that respiratory tract allergies head the list of human hypersensitivities, and particularly so with regard to their severity. Here again a mechanical factor akin to the stasis in the digestive tract may play a part. Thus a marked nasal septal deflection may offer a surface for impingement and lodging of inhaled allergens, thus to favor sensitization in those so disposed by heredity, and to provoke symptoms in the sensitized.

*The intensity of exposure to a potential sensitizing agent* is an undoubted factor in the development of sensitivity. For example, hay fever patients commonly give the history that symptoms began in that year in which they moved from the city to the country, or in the year in which they motored in early September from their home in New England to Kansas, or in a year in which pollen counts were found to be unusually high. To be emphasized in these examples is the sharp increase in, as well as the high absolute values of the exposure. The concept must be further broadened to include at times long intermissions without exposure between periods of marked exposure. Thus Cooke<sup>1</sup> has stressed the frequency of sensitization to foods that are eaten intermittently but in large amounts, such as shell fish, strawberries, mushrooms, and honey. Drug allergies commonly become manifest in patients who have been treated intensively for a time, then after an interval without treatment, were again exposed to the drug, this time with resultant symptoms.

*Increased vulnerability of the exposed surface incident to infection or trauma* involving that surface is probably an important factor in the production of sensitivity. Allergic rhinitis and asthma commonly begin after or in the course of a severe, at times protracted tracheobronchitis, such as whooping cough. The pandemic of influenza was followed by a large crop of asthma cases among the sensitizable: infection had rendered their bronchial mucosa more vulnerable; the contents of the room in which they were ill—feathers, cotton, horse hair, dust—were the things to which they were exposed and to which consequently they became sensitized. Since Schloss<sup>7</sup> in 1912 reported the case of the infant who became sensitive to cow's milk first given during a period of enteritis there has accrued both clinical and experimental evidence that sensitization takes place more easily through an inflamed than through a normal digestive tract mucosa. Fungus infection of the skin as a conditioning factor for sensitization has been referred to.

Mechanical trauma to the exposed surface may be the open sesame for the sensitizing agent. Early in his experience the writer was impressed by the fact that at least 5 per cent of hay fever patients gave the history that their trouble had started when an operation of election had been performed on the upper respiratory tract during the particular pollen season.

In short, if we have the inherited defect of becoming easily sensitized,

then operation of pure chance will determine if, when, in what portions of our bodies and to what substances we become sensitive, and the intensity of the conditioning factors will decide how early or late this will occur.

*How may prophylaxis be applied in the light of these data?*

About the most important factor, heredity, little or nothing that is practical can be done. One might advise the obviously allergic not to mate with each other, but one could not hope for any enthusiastic compliance with such advice. The suggestion has been offered (Rowe<sup>2</sup>) that if existing allergics in the parents be controlled by treatment that the offspring are less likely to inherit the defect. There is, however, no proof for such a claim and it is not in accord with known laws of genetics.

If, then, we cannot alter an individual's heredity, it follows that every effort must be made to control the factors known to influence the development of specific sensitivities.

These efforts should begin with pregnancy, if one or both parents are of clearly allergic strain. What we hope to avoid during pregnancy is the sensitization of the fetus across the placental circulation to foods in the mother's diet. To be sure, there is no proof that the measures about to be proposed will avoid such intrauterine sensitization. Some might be inclined to consider them little more than prayerful gestures. Yet if one be permitted at all to reason by analogy with other clinical experience in the development of sensitization, then the following advice, first suggested by Ratner,<sup>8</sup> is justified: The mother should avoid eating excessive amounts of any particular food, especially if this food has not been eaten for some time. It would be well that she not eat too freely at any one time of those foods which experience has shown to be good sensitizers: sea foods, nuts, raw berries, chocolate. She should be most careful not to indulge freely the dietetic whims and cravings so common in pregnancy. It would be wise to see that her diet is varied, without too much stress on any single food or group of foods. The fetus must experience what should be its guiding rule in later life: moderation in all things.

*Prevention of sensitization to inhalants* is not only the most important phase of prophylaxis but perhaps also the most satisfactory in its results, in that we are able to a considerable degree to control our environment.

This control of the environment begins in infancy. The nursery should contain as little as possible in the way of dust producers of organic origin. Infants do not need pillows to sleep on, nor does the crib need to be dressed up with a pillow by day. The mattress had perhaps better be made of a good grade of long-staple cotton (not cotton linters!) rather than hair, since sensitization seems to take place more easily to substances of animal origin. If the mattress is covered with some impervious material such as rubberized sheeting, the amount of possible dust exposure is still further reduced. Avoid soft fuzzy blankets of native wool: use instead old blankets that have been repeatedly washed, and preferably dyed, and even then place them in a bag of cotton sheeting. New sheets should be washed before use.

in order to remove substances employed in sizing. The infant should be alone in its room, but if the room is shared with another child or an adult, the bedding of the second occupant must conform in all details.

The bed room floor should be bare, or with at most a small washable cotton rag rug at the bed side. There should be no stuffed furniture and no unnecessary drapes or hangings. The walls should be painted or covered with a smooth hard-finish wall paper, and never with a rough so-called "oat meal" finish paper or with burlap. Bare plaster walls are undesirable because of the dust to which they may give rise, containing at times glue and other sizing materials. Bare walls made of various wood-pulp compositions are also to be avoided. In such a room all dusting can be done with a damp cloth.

Do not introduce any sensitizing dusts, as by spraying the room with insecticides, especially those containing pyrethrum pollen and so commonly used to kill mosquitoes. On the skin use only plain talc or stearate of zinc, not powders containing orris root or perfumes.

At this point it might be well to say something about the house in which the allergic or potentially allergic persons should live. The first point to stress is that it should be high, dry and not too much in the shade. A damp cellar favors the growth of molds whose spores in the house dust may act as sensitizing agents. The house should be heated by radiant heat, not by circulating hot air, and by a furnace burning gas or oil rather than coal. So-called "air-conditioning" devices, if they are provided with efficient filtering units, cut down dust exposure, especially to dusts from without, such as pollens. But if the air is not well filtered they may bring to a bed room, carefully furnished to avoid trouble, the undesirable dust from other rooms with upholstered furniture and heavy rugs. Old houses are perhaps more likely to suffer from the above defects than newer ones, but this is of course an individual problem.

In childhood new and important factors present themselves. There is, for example, the vexatious problem of animal pets. The child with an allergic heredity is best off without pets, or as Vaughan<sup>4</sup> suggests, may be allowed gold fish or an alligator. Yet some well-meaning relative is constantly making offers of a collie dog or a Persian cat. Such offers should be tactfully but firmly declined, at least until the time when the child is old enough not to lavish caresses on the dog or even take him to bed with him. A short-haired dog should then have the preference. It should never be permitted to enter the bed room or to lie on chairs or divans. Flea powders, especially those containing pyrethrum, are to be avoided. Best of all, no pets inside the house!

Almost as bad as live pets are woolly fuzzy stuffed toys. They are commonly made of animal hair and involve unusually intimate and prolonged contact.

As the child grows up, the precautions with regard to the bed room furnishings should not be relaxed. Cotton or kapok pillows, renewed from

time to time as their contents become old and pulverized, are to be used instead of feathers. Plain bed springs are better than box springs, the latter being just one more dust producer and the possible means of bringing in an undesirable unknown filler. There should be no compromise with the bare floor of the nursery. Yet only too often, esthetic considerations win the upper hand and deep-pile woolen rugs and carpets cover the bed room floor. Even worse than the rugs are the felt pads placed beneath them, made as they are of loosely matted hair of various animals.

In adult years the complexity of our problem obviously increases with the endless variety of possible dust exposures in everyday life. It therefore becomes necessary in large measure to consider the problem from the point of view of the individual. Nevertheless, there are a number of considerations that have a general application.

An important one is the *choice of an occupation*. Those who are sensitizable should avoid occupations that would expose them to considerable amounts of organic dusts. Yet patients are constantly making unwise selections, as did a patient of mine with allergic rhinitis who took up chicken farming and got a feather sensitization and asthma for his pains. Then there are those whose first evidence of allergy developed in the course of their work and for whom it was economically not feasible to change to other work. Black<sup>9</sup> reported the interesting case of a beauty parlor worker who became sensitive to the orris root used by her in a dry-shampoo preparation: by shifting to a buckwheat powder she got relief for a time, only to become sensitized to buckwheat. The same thing happened after she used a rye powder. When last seen she was still symptom-free while using barley flour. Sensitization of workers to organic dusts is receiving increasing attention as an industrial hazard. Thus in one large chemical plant in which some of the workers developed a skin sensitivity to phthalic anhydride, a chemical used in the manufacture of paints, it was found possible to reduce materially the number of workers becoming sensitized by suitable dust control measures.

Members of allergic families should choose their cosmetics with the possibility of sensitization in mind. Especially those containing orris root are to be avoided. Fortunately there is now available an extensive selection of such materials of known composition and made by reliable manufacturers. The less and the fewer the allergic uses in the way of all cosmetics, the better.

*Sensitization to pollens* may possibly be prevented by avoiding unnecessary excessive exposure to pollens. The sensitizable child should not play in a hay mow. The time and place of a proposed vacation should be selected with a view to possible pollen exposure. Long motor trips inland should not be undertaken at the height of the grass or ragweed seasons in June or late summer, and at these times vacations at the sea shore or the north woods are preferable to those in the country. Those of allergic strain should not live in neighborhoods in which there are large numbers of trees whose pollens are common causes of hay fever: sycamore, paper mulberry, poplar,

birch, oak. Especially to those persons who have already developed one form of pollinosis should these precautions be emphasized, lest they develop an additional type of pollen sensitivity. In fact, it is a common clinical experience when we test a patient suffering, for example, from ragweed hay fever, that he also gives a positive skin test for grass pollen, although he has had no symptoms in June. Such an individual is a potential grass hay fever candidate and should be particularly careful to guard against overexposure to grass pollen. There is ample clinical proof that disregard of this advice is followed by trouble.

*Obvious nasal defects* of the type mentioned above should be corrected as soon as the adolescent has reached an age at which an operation will no longer adversely affect facial contour in subsequent growth. But the operation should never be performed during a pollen season.

When the potential allergic travels, he will find it advantageous, and not unduly burdensome, to carry with him a cover of rubberized cloth or oiled silk to be placed on the pillow in train, hotel or guest room.

Since inhalant sensitivities would appear to arise more readily when the respiratory mucosa is rendered more vulnerable by an existing respiratory infection, all the measures to guard against sensitization should be observed with meticulous care at that time.

*Prevention of sensitization to things ingested* is on a more speculative basis than in the case of things inhaled. Yet here, too, there is reason to believe that something can be accomplished.

There is evidence to show that in infants there may occasionally arise a sensitization to foods eaten by the mother and excreted in her milk (Shannon<sup>10</sup> and O'Keefe<sup>11</sup>). It may therefore be suggested that mothers continue during lactation the precautions, mentioned earlier in this paper, to be observed with regard to their diet during pregnancy.

The common pediatric practice of boiling cow's milk before feeding it to infants should be a routine procedure, according to Pounders,<sup>12</sup> for a time with all potentially allergic infants when they are first given cow's milk. The thought is that the boiling will to some degree lessen the sensitizing capacity of the milk.

When the infant is weaned, one must keep in mind the need to avoid overeating at spasmodic intervals of certain foods. One should strive to obtain an early broad diversification of the diet. In so doing, however, one should be somewhat cautious in running counter to the violent dislikes for particular foods which the child so often expresses. One must try by tactful experiment to differentiate between the natural hesitation of most children as well as many adults to try some food never previously eaten (think of the man who ate the first snail or grasshopper) and the violent aversion that at times is an unconscious defense mechanism against a food to which the child is already sensitive. New food, when first introduced into the diet, ought to be fed in the cooked state whenever possible.

Although early diversification of the diet is desirable, it should not be



achieved by giving the young child foods that had better be withheld until later. It would be an obvious folly to give lobster, shrimp, crab or other shell fish too early, and when they are finally permitted, the youngster should not be allowed to overeat, or as the layman so well puts it, "to eat himself sick" of them. Exactly the same precautions apply to nuts and raw berries. Chocolate, a good sensitizer, should be used with discretion. Raw foods, especially raw fruits, and not excluding orange, should be used with discretion, avoiding too much daily repetition or too large quantities of the same food.

These precautions with regard to the diet in childhood should become the habits of adolescent and adult years. Particularly must the subject learn not to overindulge in those foods the intermittent supply of which is dependent on the seasons.

There are medical aspects to the possibility of preventing sensitivity to foods. In the presence of an acute digestive tract ailment, especially in the young, one should be careful not to feed too freely until the digestive upset is over. Perhaps the same caution might be wise to observe for a few weeks when the stomach or intestine has been subjected to an operative procedure. There is, however, no record of sensitization having been observed to develop postoperatively. There is also danger of precipitating sensitization if one too enthusiastically overfeeds the thin in attempting to fatten them. At the same time the physician must remember that if a diet contains too few foods, these will therefore be too often eaten and so might lead to sensitization. Yet this is just what happens to many patients who on doctor's advice or in seeking relief from digestive troubles, avoid one food after another until the dietary has become dangerously restricted. The allergist himself is only too often guilty of this mistake.

Existing functional defects which might lead to sensitization in the digestive tract should be treated or corrected. Commonest is gastric acidity. But hydrochloric acid therapy must be based on the finding of an acidity by test meal, not on the hunch of the prescriber. Stasis in stomach, duodenum or colon should be dealt with according to the usual indications.

*Prevention of sensitization to contact substances* in a measure proceeds along the lines already indicated. Moreover there is a good deal of overlapping in the matter of contact, ingestion and inhalation. The infant touches many of the things, the dust from which it also inhales. Mustard may be applied to the skin, as well as eaten. In addition to the advice already given in regard to prevention of sensitization to inhalants in infancy, consideration should be given to the things that might come into long and close contact with the skin, such as dusting powders (no orris root or lycopodium), materials of which clothing are made (silk and wool are more likely to sensitize than rayon, cotton or linen), soaps, oils and creams used on the skin (their composition should at least be known, and their effects noted). Care should be taken to avoid cheap dyes in fabrics or leather, for water-soluble or poorly fixed dyes commonly are causes of trouble.

The number and variety of contacts with substances that can lead to skin sensitization rapidly increase as the child grows. By the time adult years are reached, the problem is even more complex than in the case of inhalants. It must be approached, therefore, in the light of each individual's actual or contemplated environment.

Again, the choice of an occupation looms large; that he may avoid sensitizing contacts. But only too often advice is hard to give in this regard. Careful inquiry into the contact possibilities of a given occupation may apparently disclose no obvious sensitizers, only to be confounded by a report in the next issue of a medical journal with instances of sensitization to things hitherto believed harmless. Moreover, most industrial processes are in a constant state of change, making use of new chemicals and materials, and so introducing new and unforeseen hazards. Yet even so one may apply to advantage the principle that the dry skin is less easily sensitized than the moist.

Cosmetics, by reason of their prolonged and close contact, give rise to a great deal of skin sensitization. The variety of the substances involved may be appreciated by a glance at Goodman's text<sup>13</sup> on Cosmetic Dermatology, the first 188 pages of which are simply a dictionary of ingredients. Those who are sensitizable should therefore be exceedingly cautious in the freedom with which they use such things. As noted above, the less and the fewer cosmetics they use, the better. The same advice applies also to those who live in close contact with the potential allergic: a husband, wife, or room mate. Thus it is a common observation that a man becomes sensitive to the orris root of the face powder used by his wife, and recently one of my patients developed a contact skin sensitivity to the mustache wax used by her husband.

Since hair dyes are capable of producing marked sensitivity, they should be avoided. In fact, some boards of health require of beauty parlors that dye sensitivity be ruled out by a patch test with the dye 24 hours before the dye may be used on the head of a client. Also various dyes, especially inferior dyes, used in fabrics, in furs, and in leather articles including shoes, can sensitize the skin and so should be avoided or at least viewed with suspicion.

The possibility of *prevention of sensitization to drugs* deserves special consideration by us as physicians, for not only are we responsible for the contact with, and ingestion and inhalation of various therapeutic agents by our patients, but often enough we must needs inject into them substances which can and at times do sensitize them.

In infancy it appears to be easier to sensitize skin and mucosa than in later years. Particular thought should therefore be given to the possible sensitizing effect of preparations which we use on the infant's skin or place in its conjunctiva, nose or mouth. At all ages, if a choice is available between an inorganic and an organic drug, the former might well be selected because of the lesser likelihood of sensitization to the inorganic material.

If a drug has once been used freely and then after an interval has to be used again, its renewed application should be watched with care if that interval is over two or three weeks and less than a year, time enough for sensitization to have developed and not enough for sensitization to have worn off.

In treating the potential allergic, one should bear in mind (*a*) those drugs which experience has shown are common excitors of sensitization: aspirin, quinine, ipecac; (*b*) those drugs which give rise to serious types of allergy: malignant neutropenia from amidopyrine, and a number of other substances containing the benzene ring, such as phenacetin, acetanilid, and the arsphenamines; (*c*) those drugs whose long and habitual use, or whose recurrent use in chronic or recurrent disease could induce sensitization, such as phenolphthalein among the laxatives or cinchophen in the treatment of chronic joint troubles.

We should never use horse serum or any other foreign serum as a means of non-specific protein shock therapy, lest by so doing, we sensitize the patient to the serum and so unfit him to receive a specific immune horse serum such as diphtheria or tetanus antitoxin or antipneumococcus serum, were the need for such a serum to arise. Nor should specific serum therapy be undertaken unless the indications for its use are clear-cut and definite.

It is interesting to note that the diabetics who become sensitive to insulin and the patients with pernicious anemia who become sensitive to liver extract are usually found to be of allergic strain. There is nothing we can do to prevent their becoming sensitive, and of course we do not deny them their insulin or liver therapy merely because of the possibility of producing sensitization in them. They do, however, serve as eloquent examples of the possibility of inducing sensitivity by therapeutic procedure.

If the physician himself or the dentist, pharmacist or nurse is the potential allergic, then he should use all possible precautions to guard against sensitizing himself as he handles various drugs. This may mean the wearing of gloves to avoid direct contact when he handles these materials, or even the use of a mask to prevent the inhalation of finely powdered substances.

*Avoidance of Sensitization by passive transfer* deserves mention. Ramirez<sup>14</sup> reported the case of a man who because of acute anemia from hemorrhage was given a blood transfusion. Some weeks later the patient had his first attack of asthma on coming in contact with a horse. Investigation of the donor now showed that he was himself an asthmatic sensitive to horse dander. The recipient of the transfusion had been passively sensitized to horse dander by the circulating antibodies for horse dander in the blood of the donor. Therefore, since passive transfer of sensitivity by transfusion is possible, and since an appreciable number of individuals are allergic and therefore might have circulating antibodies in the blood, it would be wise to exclude from a blood donor's list anyone with asthma, hay fever or other obviously allergic disease.

*To whom shall the attempts at prophylaxis against hypersensitiveness be applied?*

1. *The Children of an Allergic Parent.* Especially if both parents are hypersensitive, are we justified in making every effort to prevent the development of sensitivity, since the chances are three out of four that such children will be allergic. Furthermore, the earlier in life such efforts begin the better, for the more marked the heredity factor the earlier in life on the average do these children become hypersensitive. Prophylactic advice should be given, however, whenever we see an individual with this heredity, whether he be child or adult. Thus, for example, it should be routine procedure not only in taking a medical history but in the course of so-called health examinations to inquire about allergic disease in the family history.

2. *Those Who Have Had an Allergic Disease in the Past.* The individual who has had a protracted infantile eczema, or who gives a story of a specific food idiosyncrasy or frequent attacks of hives in childhood, or hay fever in adolescence, is obviously allergic and therefore capable of developing new sensitivities.

3. *Those Who now Have Some Minor Manifestation of Allergy.* In this group the chief point of practical importance to be emphasized is this: We must recognize these manifestations as being allergic: for example, the habitual 10 or 12 consecutive sneezes, the itchy mouth whenever the patient eats certain things, the mild but definite skin rash, the indigestion, the abdominal discomfort, the diarrhea or the headache that always follows the use of a specific food, and many others with which the clinician should familiarize himself by reading an adequate text on clinical allergy.

4. *Those with Obviously Allergic Disease.* It might seem unnecessary to mention this group, whose need for prophylaxis is so self-evident. Yet it is well to remind the reader that these patients, in addition to their major allergic complaint, often have minor forms of hypersensitiveness which they fail to mention, not realizing their true significance. Thus the patient who comes to have his migraine investigated from the standpoint of possible allergy does not tell of his dozen sneezes every morning. Yet they are probably due to an allergic rhinitis that, if unrecognized and untreated, can go on to a serious asthma. Such a patient must not be tested with foods alone, on the assumption that his headaches, if allergic, are most probably due to foods. He should be tested with the usual inhalants and pollens as well. Such routine testing with a wide range of substances will often turn up skin sensitivities not yet associated with clinical symptoms, but which might under certain circumstances lead to clinical sensitivity. The testing of patients with fall hay fever by means of grass pollens as well, as mentioned earlier in this paper, is a variation of this same theme.

*How common are the individuals in whom prophylaxis against sensitization might be applicable?* It is a conservative statement to say that 15 per cent of the white population of this country is definitely allergic. At least another 10 per cent would be found, on detailed questioning, to have a minor manifestation of hypersensitiveness. The physician in his everyday practice will therefore have plenty of opportunities to put these suggestions to the test.

One might ask: Are not all human beings to some degree sensitizable? The answer is, that experimentally apparently all human beings can be sensitized. But in the great majority of instances it is hard to do so and, as far as clinical experience goes, they do not become sensitized in every day life. The 25 per cent minority, however, with their hereditary defect, are more or less easily and often sensitized, in sharp contrast to their more fortunate brethren.

### SUMMARY AND CONCLUSIONS

1. Since the underlying cause of human hypersensitiveness is unknown, no prophylaxis based on a fundamental etiology is as yet possible.

2. It is clear, however, that the victims of allergy have the characteristic of becoming sensitized to things in their environment far more easily than do normal individuals; a characteristic, in the transmission of which, heredity plays a major part.

3. Increasing clinical experience has given an insight into some of the mechanisms and conditions, by and under which the sensitization to various substances may arise.

4. In the light of such experience it seems not unreasonable to attempt, by applying the information at hand, to prevent the development of sensitivity in those predisposed thereto by heredity, and of new sensitivities in those obviously allergic.

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# CHRONIC BRUCELLOSIS (UNDULANT FEVER); AN ANALYTICAL STUDY OF THE POSITIVE RE-ACTORS AMONG SCHOOL CHILDREN \*

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THE United States Department of Agriculture in the past few years has made an extensive survey of the incidence of Bang's disease among dairy cattle in the United States. It was found that an average of 38.4 per cent of the herds tested contained positive reactors. In the infected herds 14.9 per cent were positive, of the total 11,858,859 cattle 8 per cent gave a positive agglutination test.<sup>1</sup>

Although there were reported in the United States a few scattered cases of undulant fever as early as 1904 its clinical recognition as a common infection dates from 1926. Our present knowledge of *Brucella* infection may be divided into three phases: first, the general recognition of the acute variety of the disease; second, the recognition of various complications; third, investigation of the ambulatory, subclinical and latent infections which have been classified by many observers as cases of chronic brucellosis. It occurred to us that if there is serological evidence of such wide infection in dairy cattle there should be more evidence of infection in human beings.

Therefore, we outlined a plan of study in the city of Kansas City, Kansas, for skin testing grade and high school children. While members of the State Board of Health were testing with tuberculin we applied intradermal brucellergin tests on the opposite arm. We chose children for study because they are the largest milk consumers, although the acute variety of the disease has been infrequently reported in this group. In collaboration with Baumgartner<sup>2</sup> and Lunsford 7,122 children were so tested. Divided into age groups, there were 5,809 from 10 to 19 years and 1,213 from 4 to 10. A positive allergic skin test was obtained in 642 or 9 per cent. Impressed by this rather surprising information we decided to question parents of the positive reactors about the occurrence of chronic complaints in their children. Nurses from the Health Department of the city were directed to complete a questionnaire as shown in figure 1. The nurses were carefully instructed not to ask leading questions but to ascertain as nearly as possible the present physical condition of the child. We excluded from this study 132 children who gave a simultaneous positive tuberculin test. The first questionnaire was completed in April and May of 1937. A follow-up survey was made in February 1938, in which the parents of 374 positive reactors were recontacted.

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We wish to acknowledge the coöperation of Dr. W. F. Lunsford, Director of Health, Kansas City, Kansas, and Drs. Leona Baumgartner and Alice Evans, National Institute of Health. Without their assistance the collection of this material would have been impossible.

## THIS HISTORY FOR THE PAST TWO YEARS

Name..... Address.....  
 Age..... Sex..... School Grade..... No. of other children in family.....  
 Does child drink—Raw..... Pasteurized..... Canned milk.....  
 Contact with cows (milking etc.)..... Name of dairy.....  
 Weight chart.....  
 School record—Bright..... Dull..... Medium..... Attendance.....  
 Chronic ailments.....  
 Constipation..... Temperature..... Headache.....  
 Night sweats..... Rheumatism..... Neuritis.....  
 Peculiar pain or aches.....  
 Nervous symptoms: Depression.....  
 Irritability.....  
 Tuberculin test.....  
 Are there any other members of the family ill?.....  
 Possible diagnosis.....  
 Has diagnosis and treatment of undulant fever been made?.....  
 Condition of mouth and teeth.....  
 Family physician.....

Our questionnaire was devised with the symptoms enumerated because we have encountered them frequently in chronic brucellosis. Some other symptoms frequently met with as excessive fatigue, lassitude, weakness and anorexia were omitted because of their indefinite character. The complaints recorded were chronic in nature and not those which accompanied acute or transient illnesses. When the symptoms were tabulated we combined similar symptoms into groups to eliminate duplication and to prevent undue emphasis on a single symptom as shown in table 1. Rheumatism,

TABLE I  
462 Reactors Studied

Nervous symptoms.....	208	44.3%
Headache.....	172	37.2%
Rheumatic symptoms.....	157	34.0%
Constipation.....	71	15.3%
Fever.....	22	4.8%

neuritis, aches and pains were put in a group of rheumatic symptoms. Constipation was not classified as a symptom unless it occurred concomitantly with other symptoms. The largest group was the nervous symptoms in which depression, irritability, emotional instability and other psychomotor phenomena were noted. This coincides with the frequency with which these symptoms occur in known cases of chronic brucellosis. The order of the other symptoms in frequency was headache, rheumatic complaints, constipation and fever.

Tabulations were made of the symptoms present by the first questionnaire in both the total number studied and in those who were followed. These are shown in table 2. In order to determine those in whom the symptoms were most likely to be significant of chronic illness we eliminated those who had less than two symptoms by the classification in table 1. Accordingly, of the 462 studied in 1937, 179 or 38.7 per cent had two or more

TABLE II

Number Symptoms	1937 Total	1938 Follow-up
0	116	100
1	167	135
2	80	61
3	47	35
4	32	27
5	20	16
	<hr/> 462	<hr/> 374

First group 462, two or more symptoms in 179 or 38.7%  
 Second group 374, two or more symptoms in 139 or 37.1%

symptoms while in the group of 374 followed in 1938, 139 or 37.1 per cent had two or more symptoms. The group followed then can be said to be comparable though the total is less.

From the follow-up study it was found that in 80 of the 139, symptoms persisted to some degree as shown in table 3. This represented 57.5 per

TABLE III  
1938 Follow-up

Reactors with 2 or more symptoms . . . . .	139
Symptoms persisted in . . . . .	80
Per cent . . . . .	57.5

cent of the reactors who had two or more symptoms and is a further indication of the chronicity of the complaints. Some reported additional complaints as fatigue, lassitude and anorexia. In spite of this, the majority were reported to be making satisfactory progress and gaining weight.

One hundred students of the same age group were chosen as a control. These students had negative tuberculin and negative brucellergin tests. The results of this study are shown in tables 4 and 5.

TABLE IV  
100 Control Students

Nervous symptoms . . . . .	26	26%
Headache . . . . .	15	15%
Rheumatic symptoms . . . . .	6	6%
Constipation . . . . .	2	2%
Fever . . . . .	1	1%

TABLE V  
100 Control Students

Number Symptoms	
0 . . . . .	67
1 . . . . .	20
2 . . . . .	10
3 . . . . .	3

Two or more symptoms 13 or 13%

It is apparent that there is a higher percentage (38.7 per cent) of the children with two or more symptoms in the group under investigation than



in the control group (13 per cent). It was interesting to note that many so-called normal children had chronic complaints.

*Comment.* As the result of this study it was thought advisable to secure the opinion of professors of immunology and bacteriology concerning the specificity of antibodies.

Twenty-six replies were obtained from a questionnaire asking their opinion concerning agglutinins, opsonins and allergic skin reactions for *Brucella* infection. A tabulation of their response is shown in table 6. It

TABLE VI  
Specificity of Antibodies  
26 professors

	Yes	No	Don't Know
Agglutinins.....	17	1	8
Per cent.....	65.4	3.8	30.8
Opsonins.....	8	3	15
Per cent.....	30.8	11.5	57.7
Allergic Skin.....	10	1	15
Per cent.....	38.5	3.8	57.7

was apparent that those who have had experience with *Brucella* infection believe that these clinical diagnostic procedures indicated past or present infection. We wish to make it clear that evidence of infection does not mean disease. Individuals may give positive serological or allergic evidence of *Brucella* infection with or without clinical symptoms. The diagnosis of acute or chronic brucellosis, as does the diagnosis of tuberculosis, rests upon clinical symptoms and signs plus certain immunological or bacteriological evidence. There is no group of symptoms which are characteristic of chronic brucellosis, in fact, the variety and vagueness of the complaints are features of the disease. While the symptoms encountered in the group studied may have resulted from other obscure infections or unrelated conditions, the fact that they occurred so frequently in the students with positive skin reactions warrants more than casual consideration.

Neurological complaints were found in 44.3 per cent of the reactors. This is of particular significance in view of the fact that in chronic brucellosis these complaints usually predominate.

It is not our purpose in this study to show that all of these positive reactors are actually suffering from chronic brucellosis of the ambulatory type. We are only reporting that a large number of children in the two surveys completed are suffering from chronic complaints which may be the result of *Brucella* infection. Careful clinical analysis of each individual case would be necessary to prove the above assumption. The consent of the parent and the family physician would be required to accomplish this. After consideration, we decided this would be impractical in our community.

Adequate cultural methods for the isolation of the *Brucella* are not now available. Among others, the National Institute of Health, under the direction of Dr. Alice Evans, is conducting research in this direction. When more practical laboratory procedures are devised for isolation the diagnosis of chronic brucellosis will no longer rest almost wholly upon clinical and immunological criteria. This appears to be our greatest handicap in the study of the chronic phase of the disease.

In the private practice of medicine we are too frequently confronted with patients who have definite subjective symptoms and in whom we are unable to make an adequate diagnosis. We believe with more careful clinical investigation and laboratory studies that many patients in the group referred to above could be classified as victims of chronic brucellosis. This applies not only to children but to adults.

### CONCLUSIONS

1. Evidence of chronic illness was found in 179 children or 38.7 per cent of 462 positive brucellergen, negative tuberculin reactors studied in 1937.
2. Persistence of symptoms was noted in 57.5 per cent in 1938.
3. Control studies indicated that there was a higher percentage of children with chronic illness in the group under investigation.
4. Replies received from 26 professors of immunology indicated that the presence of agglutinins, opsonins and allergic skin test are specific reactions for present or past *Brucella* infection.
5. Immunological evidence of *Brucella* infection does not mean disease. The diagnosis of chronic brucellosis depends upon clinical findings plus some positive laboratory data.
6. The ambulatory and subclinical types of *Brucella* infection are apparently not uncommon.

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# VARIATION OF BLOOD PRESSURE WITH SKELETAL MUSCLE TENSION AND RELAXATION \*

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THE welter of enumerated causes of blood pressure in health and in essential hypertension suggests that perhaps among them we have been neglecting some factor more or less familiar to all, the clear-cut recognition of which might aid us in the long run to understand problems of high blood pressure a little better. Whatever factor we suspect obviously can be better estimated if we can succeed in measuring it simultaneously with the blood pressure.†

Current opinion on the significance of vascular tonus is summarized<sup>1</sup> in a recent review by Fritz Lange.<sup>2</sup> In hypertonia the blood vessels are evidently hyperexcitable. That the arterioles together with the splanchnic arteries are mainly responsible for the regulation of blood pressure is generally conceded today. Functional constriction of these arteries appears to be the probable cause of hypertonia, or of what Hochrein terms a permanent increase in the tonus.<sup>3</sup>

Some 18 years ago clinical observations of hypertensive patients suggested that they characteristically held various skeletal muscles somewhat rigid or over-contracted or that they moved excessively, and in an experimental manner I began to train such patients to be more relaxed. The method seemed applicable to patients characteristically tense, with and without attendant high pressure, and a preliminary reference to some results was included in 1920 in an article entitled, "Use of Relaxation in Hypertensive States."<sup>4</sup>

Clinicians recognize that pressure is likely to be higher in a patient when he first walks into the office than a little later on. They note also that the pressure is likely to be higher upon admission to the hospital or on the first day or two than on subsequent days, particularly if the patient remains persistently in bed. That the blood pressure is lowered in sleep is common knowledge from the observations of Howell and others.<sup>5</sup> Such observations on patients in the clinic or at the bedside are more or less casual and generally are interpreted as variations of pressure due to emotion. Conditions are

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The experiments were conducted with the aid of William M. Lees.

† Hypertension of cardiac and renal origin lie beyond the scope of the present article.

not as a rule controlled and no attempt has been made toward distinguishing the influence of muscular tension from that of emotion.

Pertinent are the following observations made in 1929 on "Bh," whose blood pressure had been frequently recorded ever since December 1918, when he was 38 years old, and who had received a partial training in relaxation by what is called an abridged course. A portion of his earlier medical history has been published previously. He was inclined to be hypochondriac and at one time showed visceroptosis. Attacks of abdominal pain occurring prior to February 1928 and accompanied by the appearance of erythrocytes and leukocytes in the urine seemed due to ureteral spasm. A roentgen-ray examination disclosed a horse-shoe kidney. The figures recorded in table 1 were secured in 1929 with a stethoscope plus the palpatory method of taking blood pressure. Although initial pressure upon lying down is 146 systolic and 86 diastolic there occurs with continued relaxation a progressive fall during the succeeding hour of 26 mm. in systolic and 8 mm. in diastolic pressure.

TABLE I  
Blood Pressure During Relaxation in a Subject Lying Down

Position	Time (Min.)	Pressure (Mm. Hg)	Pulse
Sitting .....		140/84	
Lying .....	0	146/86	
	7	140/82	112
	37	132/80	96
	54	120/78	84

A common misapprehension is that an individual must lie down if he is to relax. The figures in table 2 are from tests with the same subject on another occasion in 1929 during relaxation in the sitting posture.

TABLE II  
Blood Pressure During Relaxation in a Subject Sitting

Position	Time (Min.)	Pressure (Mm. Hg)	Pulse
Sitting 2:00 p.m. ....	0	154/84	120
	1	154/84	
After ½ hour relaxing 2:30 p.m. ....	2	152/82	
		128/78	111
		128/78	
		132/79	
After ½ hour further sitting but not relaxing 3:00 p.m. ....		(after coughing)	
		138/78	106
		134/78	
After 1 min. clenching left fist (pressure taken on right arm) ....	1	138/78	
	2	148/84	111
	3	154/88	
		158/82	

These observations following an initial level of 154 systolic and 84 diastolic show a fall of blood pressure amounting to about 26 millimeters systolic and 6 millimeters diastolic after  $\frac{1}{2}$  hour of relaxation in a sitting position. After a further period of sitting, with instructions not to attempt to relax, the pressure rises moderately. Clenching the left fist thereafter evidently causes the pressure to rise, so that it returns to approximately the initial level.

In order to evaluate the influence of skeletal muscle tension on blood pressure we shall need to obviate or render minimal the effects of posture as well as of emotion. Another requirement for a systematic study has seemed to be an instrument capable of measuring muscular tonus accurately and in sufficiently slight states. Measuring muscle tension in intact man is no easy problem. It is not sufficient to measure contraction in muscles which are markedly rigid or which are in obvious motion; more than this, we need to be able to detect and to measure contraction in muscles which are apparently quiet; for even here the muscles may or may not be in various states of slight or moderate contraction.

No one has succeeded in overcoming these difficulties through measuring muscle tonus in intact man by mechanical means. The string galvanometer alone is not sensitive enough for the problem on hand. As early as 1922, when surface electrodes of suitable nature were attached to the flexor muscles of my own right arm, no adequate recording was secured at moments when I felt very slight contractions in that locality. Accordingly, I set out to develop or assemble apparatus which would magnify the responses obtained from the string galvanometer. This search was materially aided by the development in the amplifying power and stability of vacuum tubes due to the efforts of various physicists and radio engineers. In 1921, Forbes and Thatcher of Harvard first used an amplifying equipment together with the string galvanometer for the study of electrical changes during muscle action in man.<sup>6</sup> Since that time other investigators have used various types of similar equipment but never, I believed, sufficiently sensitive for the present type of study on muscular contraction. There is no difficulty in constructing apparatus that will give sufficient sensitivity; since adding an extra tube or more always tends to give additional magnification. But with each such addition the instrument itself becomes increasingly unstable. In consequence, the string vibrates so largely and irregularly, even when a short circuit exists across the input terminals of the amplifier, that the instrument is useless in fine measurements. Accordingly the physical problem in developing a suitable instrument centers chiefly around the elimination of sources of electrical disturbance arising both within the instrument itself and in the room or environment in which the instrument is placed. The history of the development of the instrument used in the present studies and of how disturbances were gradually reduced or eliminated has been told elsewhere.<sup>7</sup> It has proved possible to devise and assemble equipment that can be set at one thousand or more times the voltage

sensitivity of the string galvanometer as currently used in taking electrocardiograms, while the base-line shows only one or two millimeters more fluctuation than the base-line in a satisfactory electrocardiogram.

# PROCEDURE

Measurements of blood pressure and simultaneously of muscle tension by the action potential method were made in approximately 50 subjects. Approximately 38 showed normal pressure and 12 chronic vascular hypertension. Nine of the former and five of the latter had been previously trained to relax.<sup>8</sup> The subject lies comfortably in a quiet room to favor relaxation and to keep disturbing factors as far as possible constant. For shielding purposes, the couch is enclosed in a grounded metal box, but the cover can be left open and the ventilation is quite satisfactory. In a few experiments, the subject sat in a chair completely enclosed in a grounded copper screening. Electrodes consist of platinum-iridium wires, gage 22, or finer, but with sharpened points so that they penetrate the skin readily. These wires are bare for about half an inch, but are covered in their remaining portion by rubber insulating tape. This tape covers also the junction of the electrodes with the copper wires leading to the amplifier. In all of the records here to be reported, measurements are taken from the flexor muscles of the right arm. One electrode is inserted to the full length of the exposed wire into the arm flexor muscles below the nervous equator of Piper. This is called the "positive" electrode, being connected with the inner winding of the input transformer of the amplifier. The other electrode ("negative") is inserted about two inches below hypodermically in the elbow-pit in the attempt to secure a relatively indifferent location; but this attempt is far from wholly successful. In some instances a second pair of electrodes is inserted into the abdominal wall, about two inches from each other, above or below the umbilicus, but in such a line with the heart axis that a minimum record from the heart action is secured. A third pair is sometimes inserted in the left quadriceps femoris muscles, again two or three inches apart. Sometimes a fourth pair lies in the region of the right eye, one in the middle of the eyebrow and the other hypodermically about half an inch lateral to the external canthus of the right eye.

During early experiments, when two separate pairs of leads were used and I had but one recording instrument, a Cambridge string galvanometer, it was necessary to alternate, for example, taking the record from the right biceps region for a few minutes and then switching to the abdomen. At a later time, after the addition of a Sanborn outfit, two complete amplifier-galvanometer assemblies became available. Thereafter it was possible to take records solely from the biceps region as well as from the abdominal or other region selected during the entire period of experimentation; but in some experiments a changing off arrangement was used with each instrument, making it possible to secure records from four different muscular regions, each for approximately 50 per cent of the time of the study.

The photographic paper was generally run at about two inches per second or thereabouts. For purposes of economy, the shutter in one or both cameras is opened automatically by a relay device three times per minute for periods of about three seconds only. When both cameras are used, the on and off periods are identical for both.

During preparations, which take 15 minutes or more, the subject commonly lies on the couch and is encouraged to have his eyes open and to converse. But when the recording begins, he is instructed not to speak nor to open his eyes thereafter.

The presence of the electrodes in the tissues creates no noteworthy psychic disturbance and may be neglected for the purposes of the present study. There is but slight pain and this as a rule is chiefly from the initial penetration. When I have relaxed under these conditions, it has been evident that no pain continues. Previous to insertion the electrodes are immersed in 95 per cent alcohol for periods of five or ten minutes and the skin is cleansed with the same solution. The electrodes are permitted to dry in the air before insertion. While a greater dilution of the alcohol would have a higher germicidal action, I have preferred the stronger solution because it dries more rapidly. No infection has occurred.

Blood pressure is taken from the left upper arm. To eliminate subjective errors in readings the Tycos self-recording sphygmomanometer is employed as a rule. This instrument, we may assume, accurately records as a rule the systolic blood pressure, with an error which is probably negligible. The literature cited by the makers of this instrument fails to show that the diastolic readings have been sufficiently standardized. In some of the records there has been considerable doubt in my mind concerning the precise reading of diastolic pressure. Under these conditions, I present the readings for what they are worth. In the long run any errors in the recorded diastolic pressure probably do not influence the general character of our results.

With each galvanometer, string tension is set at approximately one centimeter deflection for three or four millivolts, when impressed upon the string terminals directly. From time to time throughout the period it is necessary to adjust the string tension in the Sanborn outfit so as to keep the deflection constant for a particular voltage so impressed. Such readjustments are not required with the Cambridge outfit.

We begin each period of measurement by taking in about two minutes records of the vertical time lines, occurring at intervals of one-fifth second as made with a tuning fork; of the string excursion per millivolt impressed upon its terminals; of the string excursion when one microvolt is impressed upon the input terminals of the amplifier; and of the irregular excursions of the string shadow while the amplifier input leads are short-circuited by means of a switch. Such excursions, expressed in microvolts, are one measure of the error of the instrument and, along with the width of the

string shadow, must be subtracted from the lines or magnitudes recorded during measurements of potential differences in the electrodes.

These features are illustrated in figure 1, *a, b, c, d*. In figure 1 *a* are shown a few seconds of record of action potentials from a muscle when somewhat tense. We measure in mm. the longest (vertical) line in each unit of time, 0.2 sec. From this we subtract the length of the average of the longest lines obtained from short-circuiting of the input leads of the amplifier (figure 1 *c*). The resultant is translated into microvolts (figure 1 *b*). This gives the maximum peak voltage per unit of time, 0.2 second. The average of these maxima is determined for each film exposure of several seconds and three such determinations per minute are plotted as action potentials against blood pressure in subsequent figures in this article. In a muscle completely relaxed, the vertical lines (aside from those due to the heart beats) are no longer than those present upon short circuit (compare figure 1 *d* with figure 1 *c*).

Action potentials are recorded as a rule during periods of 75 minutes or longer. Three blood pressure readings are made both initially and finally with five minute intervals. Every effort is made to be quiet and unobtrusive so as to disturb the patient as little as possible.

## RESULTS

Investigation appropriately begins with "normal" subjects not trained to relax lying down under conditions kept favorable for relaxation. The subjects were secured chiefly from the employment office of the University of Chicago. A few were from athletic teams. They ranged in age from 18 to 26 years except that one was 31. All were paid for their time. Records were discarded if the subject gave a history suggestive of hypertension. Another record was excluded on statistical grounds, as a "sport" which would distort the mean value, because the action potentials were far in excess of those of other subjects. A total of 19 records from 17 different subjects is included in the results shown in figure 2.

In this composite graph, the initial drop in pressure characteristic upon reclining does not appear, since, in order to eliminate this, blood pressure is not taken until the subject has been prone for about 15 minutes. During the subsequent interval of uninterrupted 45 minute rest, some of these untrained subjects display practically perfect relaxation often for minutes at a time in the arm flexor muscles, but less often in the abdominal group.\* However, on the average, they do not relax completely in the groups tested. Tensions range irregularly up to 2 and a little beyond, measured in microvolts and averaged. Such a state of incomplete relaxation while lying down we term "ordinary rest"; here as well as in foregoing studies, we have found that relaxation is frequently incomplete in subjects not trained to

\* Unfortunately, the number of such instances, where relaxation was attained at least in one set of muscles, as well as the number of instances of high tension, was insufficient to enable us to classify and compare the results from the two types.



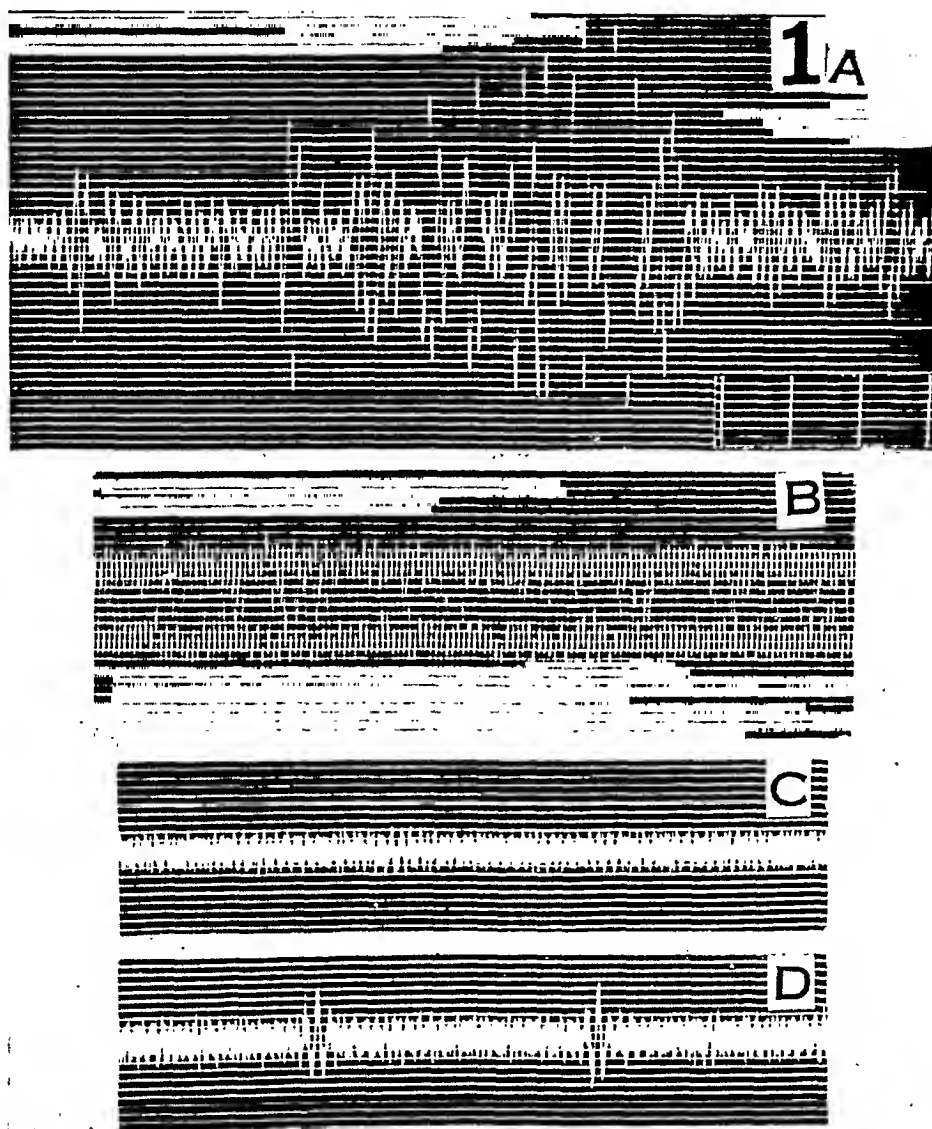


FIG. 1. *a.* Showing marked fluctuation in action-potentials from electrodes inserted into the right arm flexor muscles in a hypertensive patient lying down and attempting to relax. The greater the potentials, the greater the length of the approximately vertical lines. In right lower corner, time-lines denote intervals of 0.2 sec. They apply also to *b*, *c* and *d* of figure 1.

*b.* Calibration potential, 1 microvolt at 57 cycles per sec. Note that the overall peak excursion is approximately 15 mm.

*c.* Because of the high sensitivity, the string vibrates slightly, even when the subject is not in line but a short circuiting wire is across the input leads of the amplifier. The peak excursions shown here amount to almost 5 mm. To calculate microvoltage of each vertical line in figure 1, *a* subtract 5 from its length in mm., then divide by 5.

*d.* Showing approximately perfect relaxation (zero value of action-potentials) from electrodes inserted into the right arm flexor muscles of a patient trained to relax. The two sets of longer double lines (each almost 1 cm. long) represent heart voltages as here recorded. Intervening between these two sets, the record shows vertical lines approximately no longer than those shown in figure 1, *c*.

relax.<sup>7,9</sup> As evidenced in figure 2, ordinary rest (omitting the first 15 minutes upon change of posture) fails in the present subjects to effect any marked fall of blood pressure during the period.\* The current belief that prolonged lying down (regardless of muscle states) continues to reduce pressure is not confirmed.

In this group of 19 records from subjects with "normal" blood pressure, the initial systolic pressure (after about 15 minutes rest) is between 98 and 120 in 12 instances, which is 63.2 per cent; while the diastolic pressure is

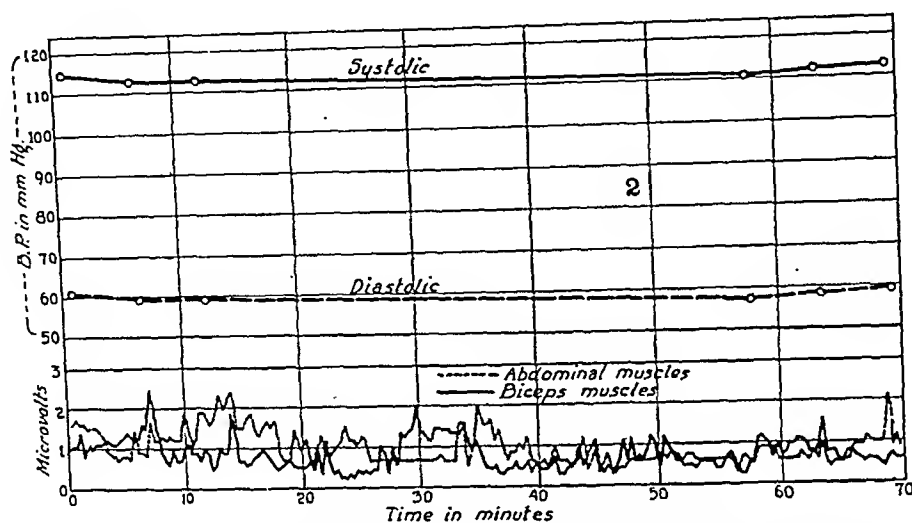


FIG. 2. Blood pressure in seventeen healthy subjects (not trained to relax) during "ordinary rest." The subjects have been lying down for about 15 minutes previously. Averages from 19 records are included, since two subjects are represented by two records. Blood pressure as well as action-potentials from abdominal and right arm-flexor muscles are plotted against time. See text for methods of recording and calculation.

As will be seen, the subjects on the average fail to relax completely, for the micro-voltages from both sets of muscles vary irregularly up to two or somewhat more. Under these conditions of moderate relaxation, which we call "ordinary rest," the blood pressure remains practically stationary during the period of seventy minutes.

between 60 and 70 in 13 instances, which is 68.4 per cent. The highest systolic pressure is 134, the lowest 89; while the highest diastolic is 75, the lowest 43. Comparing the fourth pressure reading with the initial one, the change, systolic, ranges from a fall of 11 millimeters to a rise of 7

\* It is doubtful that a difference amounting to no more than a few millimeters has any significance in blood pressure studies because the method of taking blood pressure is of limited accuracy and because blood pressure itself fluctuates in many individuals from time to time by at least a few millimeters. We note that the third reading of pressure, ten minutes after the first reading, is two millimeters less, both in systolic and diastolic pressures. Ignoring these doubts, the slight drop mentioned perhaps is a continued after-effect of the previous postural change; or perhaps it is due to the relative diminution of muscle tensions and their reflex or other effects on blood pressure; but other explanations are possible. The sixth (final) blood pressure reading is practically identical with the third. These two readings are made under analogous conditions since in each the subject presumably has been disturbed twice previously by noises of inflation and by the pressure on his arm—factors that might slightly affect the results. For similar reasons, comparing the fifth with the second reading, the values are approximately the same. It is true that the fourth reading, both systolic and diastolic, is 4 mm. below the first. If significant, this slight difference is perhaps explainable as due to the influence of the partial relaxation present during the previous prolonged rest; but the fact remains that two out of three of the readings after the 45 minute rest show practically no fall of pressure.

(excepting one instance of 23 millimeters fall); the change, diastolic, ranges from a fall of 13 to a rise of 9 millimeters.

The results with a patient not trained to relax but complaining of nervousness and restlessness are shown in figure 3. As will be seen, there was marked failure to relax, particularly in the flexor muscles of the right arm. Like the average for the subjects shown in figure 2, her blood pressure fails to fall during the 75 minute period lying down.\*

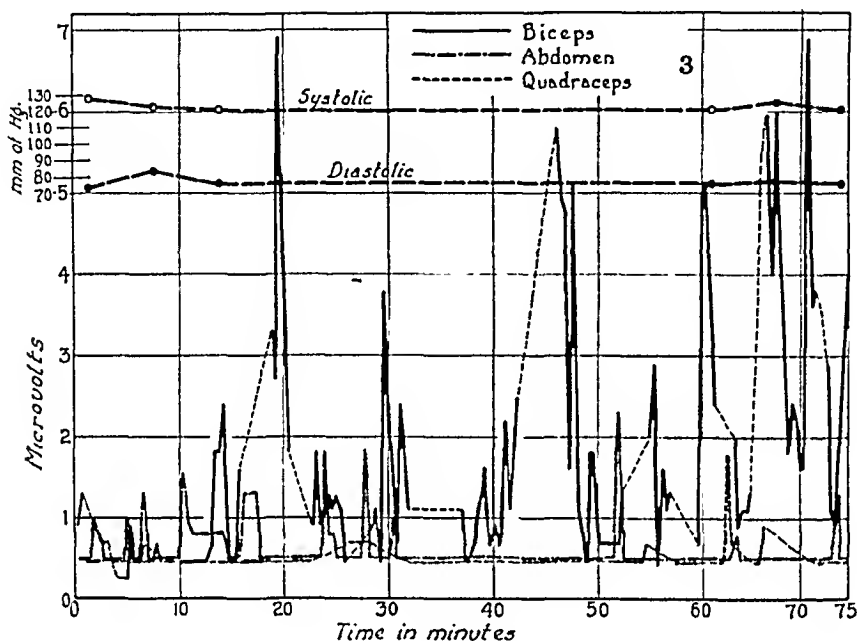


FIG. 3. Record of a nervous patient, showing failure to relax while trying to do so, lying down. Time in minutes begins at 0, when she has already been resting for about 15 minutes previously. In the right arm-flexor muscles, microvoltages vary greatly, at times almost reaching seven. However, the abdominal muscles show less microvoltage, often remaining continuously at about one-half and seldom beyond two. Likewise, the left quadriceps muscles show still less microvoltage, often remaining continuously at about one-half and seldom beyond one. (For the abdominal musculature in this graph, recording is performed continuously with the Cambridge outfit by the sampling method described in the text. However, the recording from the biceps muscles with the Sanborn outfit is interrupted at the times indicated by lighter broken lines connecting the heavier continuous ones. At such times is taken the record for the left quadriceps muscles.)

During this 75 minutes with relaxation incomplete, the blood pressure remains practically stationary.

The influence of relaxation is conveniently studied in patients trained to relax. "Ve," who complained in 1930 of spells of stammering and stuttering and occasionally manifested symptoms evidently due to an irritable colon, had normal blood pressure. Although trained to relax he did not meet with equal degrees of success on all occasions.

\* I am grateful to Dr. A. T. Kenyon of the University of Chicago Clinics for referring this patient and for the following notes: She complains also of pains in the head, right flank and elsewhere. Thyroidectomy four years previously, but basal metabolism now +1 per cent. She dates her present symptoms from pregnancy, fourteen months ago. No organic pathology found, except marked lumbar lordosis. Wassermann and Kahn negative; hemoglobin, 80 per cent, red blood cells, 4,230,000; urine, negative.

In figure 4 are graphed the results for the half-hour period, when the subject appears to lie very quietly, showing no tension grossly manifest to the naked eye. Action potentials from the right arm flexors continue approximately at zero level throughout. It is unusual in my experience for a patient to show such prolonged, uninterrupted relaxation in a muscle group unless trained to relax. Nevertheless the record shows that the abdominal muscles fail to relax completely; at certain moments the peak microvoltage reaches 12. Notwithstanding the advanced degree of relaxation in the arm flexors, the systolic blood pressure ranges from 120 to 114 and the diastolic from 77 to 60, which is about on the same level as when he lies down in

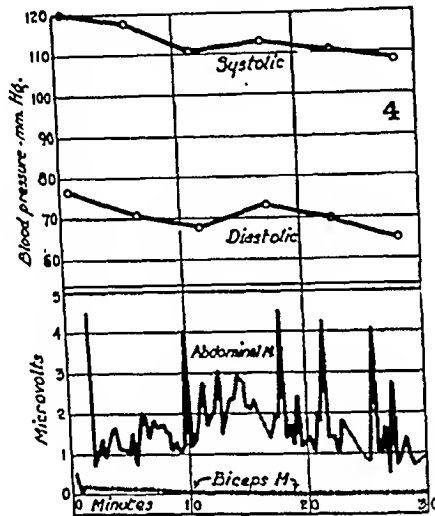


FIG. 4. Partially successful relaxation in a nervous patient previously trained to relax. "Time in minutes" begins at 0, when he has already been lying down for about fifteen minutes previously. Relaxation continues practically complete in the right arm-flexor muscles throughout the record. However, he fails to relax the abdominal musculature, for the microvoltage seldom falls below 1 and often exceeds 4.

Blood pressure readings are made every five minutes, showing a slight fall toward the end of the thirty minute period. The range is from 120/76 to 108/65.

ordinary rest and at times clenches his fist, as shown by another record not here presented.

Upon the occasion represented in figure 5, however, relaxation is evidently more generalized than in figure 4 and there is lower pressure, both systolic and diastolic. After the pressure is once taken, the microvoltage of the right arm flexors continues at approximately zero, while that of the abdominal and of the left quadriceps femoris muscles seldom reaches and never exceeds one. An exception to this statement is the time (approximately at 21 minutes) when he falls asleep and evidently loses conscious control of his muscular states, whereupon the microvoltage of the right arm flexors becomes almost 5. This rise is but momentary, for, upon being awakened, he quickly regains control and relaxes promptly. Throughout the record in figure 5, the systolic pressure ranges from approximately 105 to 100, which is 15 to 14 mm. below the range in figure 4. The consideration

that blood pressure varies somewhat even in the same individual from day to day would not justify us to cast aside these data, if only because we are here engaged in determining some of the factors that evidently are responsible for such fluctuations. On several other occasions when this subject was not so completely relaxed, the pressure was notably higher. A fall is seen also in the diastolic pressure (*vide supra*), since the range in figure 5 is from 59 to 52 mm. in contrast with 77 to 60, a reduction ranging from about 18 to 8 millimeters.

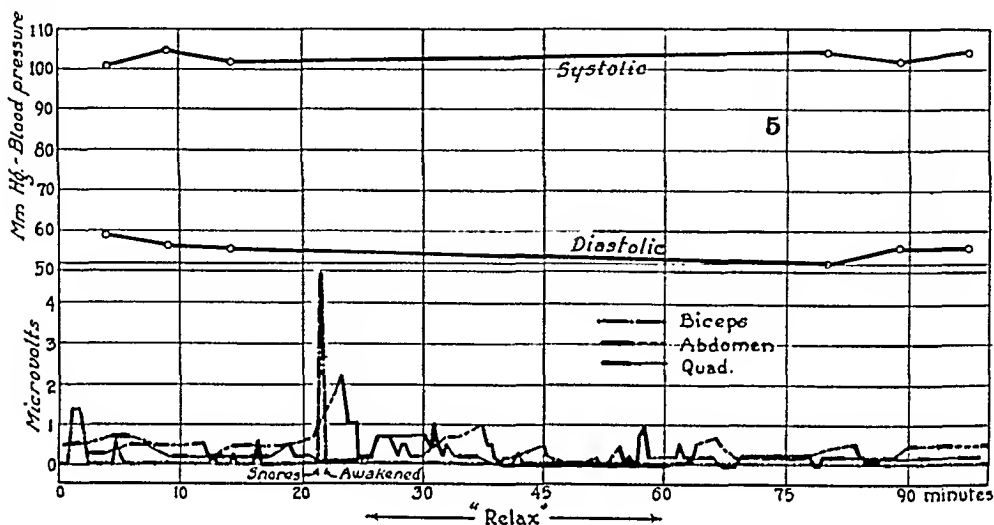


FIG. 5. More successful relaxation in the same patient on another occasion, as compared with figure 4. The right arm-flexor muscles, recorded continuously by the sampling method with the Sanborn outfit, show an absence of action-potentials practically complete, except at one time (about 21 minutes after the beginning of the record, which is about 36 minutes after he lies down). At this time he falls asleep and action-potentials appear, mounting above 4 in microvolts. Upon being awakened, he quickly regains control and relaxes again promptly and completely. Aside from this moment of going to sleep, action-potentials from the abdominal and right quadriceps muscles range at times up to 1 microvolt, but in general at about one-half microvolt or below.

Under these conditions, the blood pressure remains approximately stationary during the ninety minute period of observation, but the range is 105/59 to 102/50. This range is distinctly lower than that in figure 4, at least in so far as the maximum systolic pressure is 15 mm. less than that in figure 4 and the maximum diastolic pressure is 16 mm. less than that in figure 4. While the lowering is less marked in the comparison of minimum pressures, the results indicate a difference which is probably significant and is most likely due to the influence of relaxation rather than to coincidence.

If, as we assume, the essential feature in figure 5 as compared with figure 4 is that the subject relaxes the abdominal muscles more fully, this is attended by a markedly lower diastolic as well as systolic pressure. Although the decrement in tension, considering the musculature as a whole, is small, the reduction in pressure is marked.

A much greater decrement in microvolts, if it occurs when the subject is generally much more tense as shown by electrical measurements, may fail to be accompanied by such a marked lowering of pressure.

These results need to be confirmed. They suggest that blood pressure drops with muscle-tension, but not proportionally; rather, the drop in pres-

sure is most marked if tensions have been previously reduced, especially if to the neighborhood of zero.

According to results so far considered, prolonged rest effects no marked reduction in pressure after the initial drop due to change of posture, not only if the subject remains more or less tense (while the variations in tension from time to time remain on about the same order) throughout the period (figures 2, 3 and 4); but also if he continues from the outset to be very well relaxed (figure 5). The intermediate condition, next to be considered, is where the subjects on the whole become more relaxed during the period or towards its close than they were at the outset. This condition probably occurs in most of the results considered in table 3, although an examination of the individual records falls short of furnishing proof that it prevails throughout the musculature of each subject.

Table 3 includes 10 subjects with normal blood pressure and four with essential hypertension. Only seven of the former group had been trained to relax; Ny and Ad were athletes belonging to University teams and were selected for the present studies after their ability to relax had been demonstrated in electrical tests.

We expect a fall of pressure in many or most instances in the first 10 or 15 minutes after lying down. The record of this preliminary fall is eliminated from table 3, since the initial reading is some 15 minutes or more after the change in posture. If after the pressure is thus lowered at the outset, a still further fall is found to occur with relaxation, even if not very large, it is likely to be significant since the amount of this fall added to the amount of the fall evoked upon change of posture may constitute a marked fraction of the pressure originally present before change of posture.

In the subjects with normal pressure, but not trained to relax, partial relaxation is attended by an average fall of about 5.6 and 7.2 millimeters respectively in systolic and diastolic pressure,\* which is in addition to the initial fall effected upon change from standing or sitting to lying down. A somewhat greater average fall, namely about 12 or 13 millimeters both systolic and diastolic occurs in six instances out of nine in subjects with normal pressure but trained to relax; and a still greater average fall of systolic pressure in essential hypertension occurs in two out of three subjects partly trained to relax (namely about 22 millimeters). The number of tests represented in the studies of table 3 and table 4 is in a sense insufficient to warrant final conclusions, especially if these studies are considered apart from the other studies reported in the present and in following articles. However, careful inspection of the results in these tables nevertheless reveals a trend very clearly.

Figure 6 illustrates a record in hypertension. It is from the patient "Bh," observations on whom were discussed on page 1195. The influence

\* This average includes only those instances in which a fall occurred and is based upon differences between the first and fourth readings. It should be noted that the analogous average from the "normal" untrained subjects in figure 2 has practically the same value.

TABLE III  
Measurements of Blood Pressure and of Muscle Voltage in the Supine Posture, with Relaxation Generally Increasing  
NORMAL BLOOD PRESSURE

Subjects not Trained	Date	Blood Pressure, mm.		Muscle Microvoltage					
		Before Rel.	After Rel.	0-15 Min.	15-30 Min.	30-45 Min.	45-60 Min.	60-75 Min.	
Ny. <sup>20</sup> ♂	2/28/34	125/67	119/55	Arm: 0 to 0.5 (0.7) <sup>1</sup> Abd: 0.9 to 1.4	0 to 0.2 0.6 to 1.1	0 to 0.2 (3.0) <sup>1</sup> 0 to 0.6	0 to 0.2 (0.5) <sup>2</sup> 0 to 0.9 (1.4) <sup>2</sup>	0 to 0.2 (1.5) <sup>1</sup> 0 to 1.7	
Ny. <sup>20</sup> ♂	3/14/34	127/75	125/70	Arm: 0 to 0.2 (0.8) <sup>1</sup> Quad: 0 to 0.7	0 to 0.2 (2.9) <sup>1</sup> 0.5 to 1.9	0 to 1.3 (4.3) <sup>1</sup> 0 to 0.8 (3.8) <sup>1</sup>	0 to 0.1 0 to 0.5 (5.2) <sup>1</sup>	0 to 0.7	
Ad. <sup>20</sup> ♂	3/ 7/34	113/63	105/55	Arm: 0 to 0.9 (1.7) <sup>1</sup> Abd: 1.0 to 2.8	0 to 0.3 (2.3) <sup>2</sup> 1.8 to 2.5	0 to 0.3 1.2 to 2.2	0 0.8 to 1.8 (2.0) <sup>2</sup>	0 (2.3) <sup>2</sup> (3.4) <sup>1</sup> 0.8 to 1.5 (2.2) <sup>2</sup>	
Ad. <sup>20</sup> ♂	3/14/34	118/61	113/63	Arm: 0 to 0.4 (0.7) <sup>1</sup> (8.2) <sup>1</sup> Quad: 0	0 to 0.4 (13.3) <sup>1</sup> 0 to 0.7 (1.7) <sup>1</sup>	0 to 0.2 (8.7) <sup>1</sup> 0 to 0.7 (1.0) <sup>2</sup>	0 to 0.2 (9.3) <sup>1</sup> (13.3) <sup>2</sup> 0.3	0 to 0.2 0.3	
Ba. <sup>22</sup> ♂	3/ 8/34	127/75	120/62	Arm: 0 to 4.6 Abd: 0 to 0.7 (1.0) <sup>2</sup>	0 0.7 to 1.3	0 0.3 to 14.3 (20.0) <sup>2</sup>	0 0 to 4.3 (9.7) <sup>2</sup>	0 0	
Trained Et. <sup>21</sup> ♂	3/ 3/34	137/90	129/77	Arm: 0 to 0.3 Eye: 12.0 to 19.0	0 9.0 to 13.0	0 8.0 to 15.0 (46.0) <sup>1</sup>	0 (0.2) <sup>1</sup> 4.0 to 19.0 (23.0) <sup>1</sup>	0 (0.3) <sup>2</sup> 8.0 to 15.0 (20.0) <sup>1</sup>	
Et. <sup>21</sup> ♂	3/ 8/34	115/67	108/68	Arm: 0 to 0.5 Eye: 6.0 to 13.0	0 to 0.5 6.0 to 8.0	0 to 0.5 5.0 to 9.0	0 to 0.5 (0.8) <sup>1</sup> 6.0 to 10.0	0 to 0.5 8.0 to 10.0	
Et. <sup>21</sup> ♂	3/17/34	110/60	98/60	Arm: 0.3 to 0.5 Quad: 0 to 0.1 Eye: 5.0 to 15.0	0 to 0.5 0.3 to 0.1 2.0 to 9.0	0.3 to 0.5 (5.11) <sup>1</sup> 0.5 9.0 to 15.0	0 to 0.3 0 to 0.5 2.0 to 15.0+	0 to 0.3 0.2 to 0.6 4.0 to 15.0	
Ro. <sup>24</sup> ♀	3/15/34	129/79	111/72	Arm: 0.5 to 4.4 Quad: 0.2 to 0.4 Eye: 18.0 to 34.0	0.3 to 1.2 0.2 to 0.4 10.0 to 16.0	0 to 0.9 (2.1) <sup>1</sup> 0.5 to 0.7 10.0 to 19.0	0.3 to 1.5 5.0 to 12.0	0.5 to 0.7 (4.2) <sup>1</sup> <sup>2</sup>	
Ka. <sup>26</sup> ♂	3/17/34	126/83	114/65	Arm: 0 to 5.8 Quad: 0.5 to 0.7 Eye: 14.3+	0.9 to 3.2 (5.4) <sup>2</sup> 0.7 to 1.0 14.3+	0.3 to 1.0 0.7 to 1.0 14.3+			
Lu. <sup>27</sup> ♂	3/14/34	132/88	135/88	Arm: 0 to 0.2 Quad: 0 to 1.3	0 to 0.2 0 to 0.7	0 to 0.2 (0.4) <sup>1</sup> 0.3 to 1.2 (3.1) <sup>1</sup>	0 to 0.5 0.7 to 1.4 (6.3) <sup>2</sup>	0 to 0.2 0 to 0.7	
Di. <sup>27</sup> ♂	3/ 1/34	138/80	128/75	Arm: 0.5 to 1.2 (2.5) <sup>1</sup> Abd: 0	0 to 0.3 0 to 0.2	0.3 to 0.9 (11.4) <sup>2</sup> 0	0.3 to 1.0	0.2 to 0.5 (4.1) <sup>2</sup> 0	
Ve. <sup>28</sup> ♂	2/ 9/35	123/75	104/50	Arm: 0.5 to 1.0 (15.0) <sup>1</sup> Quad: 0.2 to 0.5 Abd: 0 to 0.5	0.3 to 0.5 0.2 to 0.5 0 to 0.5	0 to 0.4 0.2 to 0.5 0 to 0.5	0 to 1.1 (3.8) <sup>2</sup> 0.2 to 0.5 0 to 0.5		
Bn. <sup>40</sup> ♂	2/ 4/35	117/63	116/57	Arm: 0 to 0.2 (4.3) <sup>2</sup> Quad: 0.2 to 2.0 Abd: 0 to 0.2	0 to 0.4 0 to 0.2 (3.5)	0 to 1.2 0 to 0.4	0 to 0.5 0 to 0.4	0 to 0.5 0 to 0.4	

TABLE III (Continued)  
ESSENTIAL HYPERTENSION

Not Trained	Date	Blood Pressure, mm.			Muscle Microvoltage				
		Before Rel.	After Rel.	Fall	0-15 Min.	15-30 Min.	30-45 Min.	45-60 Min.	60-75 Min.
Ch. <sup>10</sup> ♂	9/24/36	160/92	160/83	0/9	Arm: 1.0 to 2.3 (6.0) <sup>1</sup> (20.0) <sup>20</sup> Abd: 0.8 to 1.2 (2.8) <sup>3</sup>	1.0 to 4.0 (7.3) <sup>1</sup> 0.8 (1.2) <sup>2</sup>	1.0 to 4.3 (0.7) <sup>2</sup> 0.4 to 0.8	0.7 0.4 (0.8) <sup>2</sup>	0.7 (1.7) <sup>2</sup> 0.4 (0.8) <sup>4</sup>
Partly Trained Bh. <sup>10</sup> ♂	12/ 9/33	180/97	155/95	25/2	Arm: 0.3 to 3.0 Abd: 1.3 to 3.2	0.3 to 3.7 0.3 to 5.1 (15.0) <sup>1</sup>	0.5 to 1.5		
Bc. <sup>10</sup> ♂	2/ 8/34	175/106	155/94	20/12	Arm: 0.3 to 3.2 Abd: 1.7 to 3.2 (15.0) <sup>1</sup>	0.2 to 6.3 1.3 to 2.4	0.2 to 3.6 0.5 to 2.0		
Ma. <sup>10</sup> ♂	1/12/34	172/82	165/68	7/14	Arm: 0.2 to 3.8 (5.8) <sup>2</sup> Abd: 1.3 to 4.2	0.8 to 1.4 1.1 to 2.7 (4.8) <sup>1</sup>	0 to 3.4 1.4 to 2.4 (3.5) <sup>1</sup>		

After stating the range in microvoltage in the last five columns, additional figures in parentheses denote variation from the range, where this occurred. Each coefficient denotes how many times the variation occurred. For example, since three determinations are made per minute, the coefficient "1" in the column, "30-45 Min.," indicates that the value in parentheses was determined during that period only once. The coefficient "X" denotes that the deviation was sustained practically constantly during the last portion of the period.



of fair relaxation is exemplified in the right arm flexor muscles during the first twenty-eight minutes; the pressure falls from 170 systolic and 87 diastolic (read after about 15 minutes lying) to 135 systolic and 80 diastolic. Pressure remains lowered and arm microvoltages do not increase much during conversation with him about an indifferent subject, the World's Fair. However, upon discussing the prospect of his aunt's death, about which he was greatly concerned, action potentials increase greatly in his arm muscles attended perhaps by a moderate rise in pressure, although the results here are not very marked. Upon resumption of chat about the World's Fair, the arm tensions diminish and perhaps the blood pressure somewhat also.

TABLE IV  
Summary from Table 3.  
NORMAL BLOOD PRESSURE

Subjects	Total Tests	No. Reduced	Aver. Reduction	Reduction in $\frac{2}{3}$ Cases
Not Trained.....	5	Systolic 5 Diastolic 4	5.6 7.2	
Trained.....	9	Systolic 8 Diastolic 8	9.3 8.8	13.3 12.3
ESSENTIAL HYPERTENSION				
Partly Trained.....	3	Systolic 3 Diastolic 3	17.3 9.3	22.5 7.0
TOTAL RESULTS				
All Tests.....	17	Systolic 16 Diastolic 15		

The results for subject Ch. are not included in this table.

However, after 45 minutes he begins to be concerned about a full bladder and his arm tensions mount conspicuously \*; at 60 minutes the microvoltage exceeds 14. At this point the blood pressure has returned to the levels observed toward the start, terminating even slightly higher, 175 systolic and 90 diastolic. As will be noted, the increment of microvoltage from the arm muscles at the termination is out of proportion to the increment of blood pressure. This again illustrates the correlation discussed previously.

A control test in a patient with essential hypertension who fails to relax appears in figure 7. No decline is seen such as occurs with prolonged relaxation and the course of blood pressure is fairly irregular. Similar results were observed in two other hypertensive subjects.

\* In another hypertensive individual disturbed by a full bladder, I have recorded a similar marked rise in pressure.

## COMMENT

Since it is generally admitted that posture and emotion influence blood pressure, the aim in the present studies has been to render these influences constant so far as possible. Measurement of the neuromuscular elements has indicated that a quantitative relationship commonly prevails between the degree and duration of relaxation and the fall in pressure effected. However, this relationship is not a proportional one: generally speaking, under

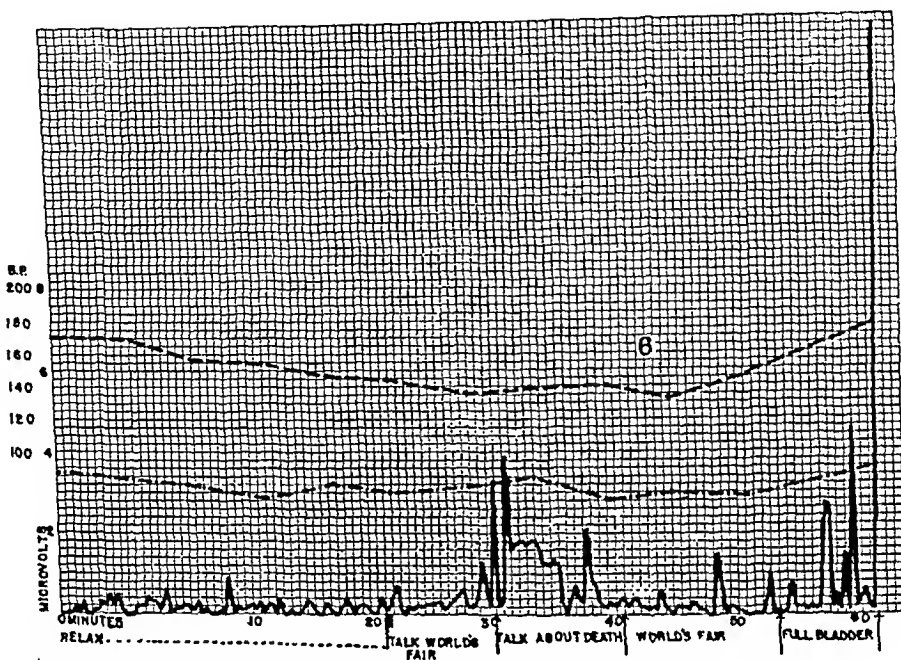


FIG. 6. Partial relaxation, moderate arterial hypertension, in a man 54, somewhat trained to relax. He has been resting for more than 15 minutes before the record is begun at "0 minutes." From 0 to 29 minutes of the record, relaxation in the right arm-flexors is fair, generally below  $\frac{1}{2}$  microvolt, with occasional peaks under 1. During this interval, blood pressure falls on the whole, from an initial 170/87 to about 135/80. In the period, 22 to 29 minutes, he converses about the World's Fair, evidently without becoming tense. From 29 to about 39 minutes, the investigator discusses with him a topic known to be exciting at the time, whereupon the action-potentials measured increase markedly, and there is perhaps some moderate corresponding increase in pressure, but this is not certain. With the decrease in action-potentials observed in the interval from 40 to 52 minutes, during which discussion concerning the World's Fair is resumed, a moderate decline in pressure probably again appears, but this decline, if present, most evidently gives place to the beginning of a marked rise in microvoltage as well as in pressure, evidently owing to sensations from a full bladder, about which he expressed mounting concern. While he finally becomes very tense, microvoltage above 14, the blood pressure increases markedly, but not proportionally.

present conditions, the fall in pressure which accompanies a slight decrease in tension becomes greater as relaxation becomes approximately complete.<sup>10</sup>

In accordance with the experience of most clinicians, we should expect a noteworthy drop in pressure to take place in the first 15 minutes of rest. This expectation was confirmed when the pressure was taken before the patient lay down to rest. We omitted taking the pressure during the first 15 minutes of rest because we did not wish to disturb the patient unnecessarily.

According to the present results, not merely systolic pressure varies with the state of skeletal musculature but diastolic pressure as well. Variation of diastolic pressure with the state of tension has been found not only with the Tyco's instrument, but also upon auscultation with the stethoscope. Both diastolic and systolic phases have tended to fall with advancing relaxation. In general, the findings suggest that blood pressure tends to vary to a certain extent with the tension in the total mass of skeletal musculature; but the possibility remains that certain muscle groups are of particular moment, specifically the abdominal muscles.

If blood pressure varies with skeletal muscle tension and relaxation, this may conceivably be due to associated tension and relaxation of the muscle fibers in the arterioles and the muscular arteries. Lower pressure might

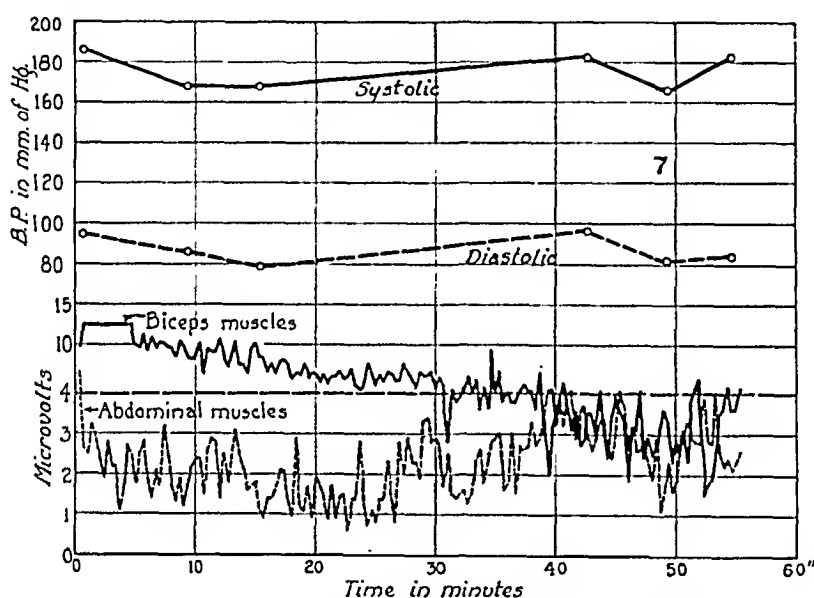


FIG. 7. Failure to relax, arterial hypertension, in a patient not trained to relax. The blood pressure remains up.

result from diminution of tonus, in the sense of Fritz Lange, as discussed above. Another mechanism might be reduction in the force and rate of the heart-beat brought about upon relaxation. Consideration of these possibilities is deferred to a later article.

There has been a traditional belief that healthy muscle, even at rest, is always in slight contraction. This view has rested upon inference. The present methods have afforded the first opportunity to test its accuracy; but have failed to confirm it. I have found in healthy man, as well as in animals, that action potentials (a sign of contraction) are completely absent in muscle fully at rest.<sup>11</sup>

#### SUMMARY AND CONCLUSIONS

1. It is known that blood pressure varies with emotion and with change of posture; but aside from casual clinical observations, no study to ascertain

whether blood pressure varies specifically with skeletal muscle tension has heretofore been made.

2. Quantitative studies of skeletal muscle contraction have been made possible through the development of very low voltage measuring apparatus. Some of the history of this development is recounted. Measurements were secured most commonly in the right arm flexor muscles, the abdominal muscles and the left quadriceps femoral.

3. Preliminary studies were made with the auscultatory method of taking blood pressure; later ones with the Tycos self-recording sphygmomanometer\* in order to eliminate the subjective factor in taking blood pressure. To minimize the effects of change of posture upon the blood pressure recorded, the initial reading was not taken until the subject had reclined quietly for about 15 minutes.

4. Records were secured from 17 subjects with "normal" pressure not trained to relax, but while lying at rest. They confirm the findings in previous studies that individuals lying down do not necessarily relax; their various muscles may show varying frequencies and magnitudes of action potentials. During such moderate relaxation, no marked fall of blood pressure occurs.

5. Also, if there is marked failure to relax while reclining, the pressure does not fall.

6. The findings suggest that blood pressure tends to fall with decline in skeletal muscle tension, but not proportionally. The greatest fall, both systolic and diastolic, relative to the amount of tension relaxed, evidently occurs in the range where muscle contraction is slight and is then further reduced.

7. Under present conditions, blood pressure appears to remain approximately stationary during the rest period (beginning 15 minutes after change of posture), if the patient remains relaxed throughout, when it is at a relatively low level for that individual; but approximately stationary also, although at a higher level, if his muscles continue somewhat tense throughout and the fluctuations are not greatly at variance.

8. Greater falls in blood pressure, both systolic and diastolic, measured in millimeters often occur when relaxation takes place during or towards the end of the rest period, than when such relaxation is observed from the outset. No such fall commonly occurs in the hypertensive subject if he persistently fails to relax.

9. An initial drop in pressure commonly follows change to the lying posture. Thereafter an additional fall in pressure often occurs, evidently due to relaxation. The sum of these two decrements may constitute a considerable percentage of the initial pressure—a consideration which adds weight to the figure for the fall effected upon relaxation.

\* The systolic readings with this instrument are probably more reliable than are measurements made with the aid of the stethoscope. Unfortunately, the diastolic measurements with this instrument have not been standardized; however, for the comparative purposes of the present studies, they appear to be fairly satisfactory.

10. The findings furnish foundation for the view that high blood pressure in essential hypertension can result in part from habitual activity involving hypertensive states in the skeletal musculature.

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# HUMAN AUTONOMIC PHARMACOLOGY

## XV. THE EFFECT OF ACETYL-BETA-METHYLCHOLINE CHLORIDE (MECHOLYL) BY IONTOPHORESIS ON ARTERIAL HYPERTENSION \*

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IN previous experiments<sup>1, 2</sup> on the pharmacology of the autonomic nervous system, it was found that the blood pressure elevation produced by benzedrine sulfate (benzylmethyl carbinamine or beta-phenyl-isopropylamine) was quickly lowered by an injection of mecholyl (acetyl-beta-methylcholine chloride). This effect was of short duration, the blood pressure quickly resuming the high level produced by the benzedrine.

In the present study, our aim was to compare the blood pressure lowering effect of mecholyl iontophoresis on benzedrine-induced hypertension and on senile hypertension.

The technic of mecholyl iontophoresis has been described by many authors, including ourselves.<sup>3, 4, 5, 6, 7</sup> The drug is introduced into the organism via the skin by means of the galvanic current through the positive electrode saturated with 1 per cent mecholyl solution at a milliamperage varying from 5 to 30. The strength of the current is varied, according to the reaction of the individual subject to mecholyl. In most instances, the positive electrode was applied to the abdomen and the negative electrode to the back; in others, the thigh or the leg was used. Wire gauze electrodes enclosed in flannel bags were found most convenient, since they readily conformed to the contour of the part to which they were applied. Greater absorption of the mecholyl seemed to occur over the abdomen than on the thigh or leg. When the iontophoresis was continued for longer than one hour, the electrodes were resaturated with the mecholyl and salt solutions respectively.

The experiments were carried out on the following groups of subjects: (1) a group of 10 dementia praecox subjects whose cardiovascular systems were apparently normal and in whom a hypertension was produced by intramuscular injections of benzedrine sulfate (40 to 50 mg.); (2) a group of 8 senile subjects exhibiting varying degrees of hypertension; and (3) a group of 7 senile hypertensives in whom the iontophoresis was preceded by the administration of prostigmin (dimethylcarbamate ester of *m*-oxyphenyltrimethylammonium methylsulfate), 0.5 mg. subcutaneously.

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From the Division of Psychiatric Research, Boston State Hospital, Mattapan, Mass., aided by grants from the Commonwealth of Massachusetts and the Rockefeller Foundation.

## RESULTS

1. *Effect of mecholyl iontophoresis on the hypertension produced by benzedrine:* Table 1 gives the important data in regard to the blood pressure

TABLE I

The Effect of Mecholyl Iontophoresis on the Hypertension Produced by Benzedrine  
(10 Cases of Dementia Praecox)

Case	Before Iontophoresis				Period of Iontophoresis			After Iontophoresis	
			Ht. of Benzedrine Reaction		Ht. of ABC* Reaction			(Within 2 minutes)	
	Initial B.P.	Pulse	B.P.	Pulse	Minimum B.P.	Time†	Pulse	Final B.P.	Pulse
G. T.....	124/80	64	184/90	54	136/70	60 min.	88	158/88	64
J. M.....	156/90	88	214/114	64	156/92	60 "	100	200/108	68
L. G.....	98/66	68	160/95	56	122/78	90 "	64	150/90	54
G. T.....	134/82	68	176/88	60	144/68	30 "	88	162/90	60
L. G.....	100/60	78	158/98	60	100/50	75 "	100	140/88	56
M. G.....	130/88	84	200/110	68	120/80	57 "	108	190/102	62
A. W.....	130/66	96	152/70	76	116/50	30 "	108	148/70	76
E. J.....	136/90	84	178/98	70	152/84	30 "	84	174/100	64
J. G.....	120/72	56	180/100	56	140/82	35 "	88	170/106	66
A. McN..	116/80	86	150/96	76	120/82	37 "	84	144/96	72

\* Acetyl-beta-methylcholine chloride (mecholyl).

† Length of time normal blood pressure maintained.

and pulse changes in this group of experiments. (a) The basal blood pressure of the 10 subjects ranged from 98 mm. of mercury systolic and 66 diastolic (98/66) to 156 mm. systolic and 90 diastolic (156/90). The maximum blood pressure readings, following the administration of benzedrine, varied from 150/96 to 214/104, with an average systolic rise of 51 mm. and an average diastolic rise of 19 mm. Accompanying these changes in blood pressure, there was a fall in pulse rate in nine of the cases, varying from 8 to 24 beats per minute; in the other case, no change in pulse rate occurred. (b) The fall in blood pressure during the period of mecholyl iontophoresis was gradual and reached its lowest levels in from 13 to 56 minutes. The decrease in pressure varied from 26 to 80 mm. systolic and from 12 to 48 mm. diastolic, with an average systolic decrease of 45 mm. and an average diastolic decrease of 21 mm. During the period of reduced blood pressure, the pulse showed an average increase of 27 beats per minute, varying from 8 to 40 beats per minute. In only two cases did the pulse go above 100; in all instances, it remained regular and of good quality. Once the blood pressure had reached a low level, the iontophoresis was continued from 30 to 90 minutes, maintaining a normal or low level of blood pressure readings

during that time. Upon cessation of the current, the blood pressure returned to previous levels in from 5 to 15 minutes. In most instances, there occurred flush and mild perspiration of the face and sometimes of the chest, slight lacrimation, and audible intestinal peristalsis. Until these phenomena occurred, there was little or no effect on the blood pressure. Iontophoresis with mecholyl was regularly effective in lowering the hypertension produced by benzedrine to normal levels. In two cases, furthermore, the iontophoresis applied before the administration of benzedrine prevented a rise in blood pressure so long as it was continued (charts 1 and 2).

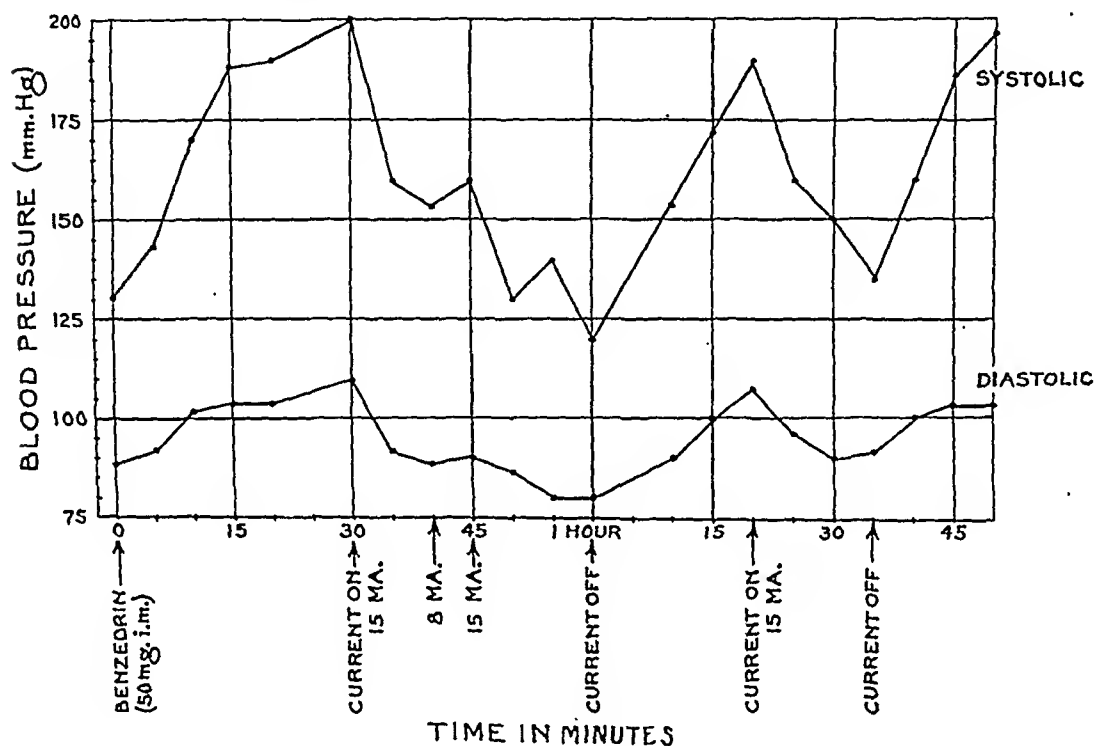


CHART 1 (Case M. G.): The effect of mecholyl iontophoresis on the hypertension produced by benzedrine. The blood pressure was very effectively reduced to normal levels and quickly returned to a high level when the current was discontinued.

2. *The effect of mecholyl iontophoresis on eight subjects with senile hypertension* (table 2, charts 3 and 4): These subjects varied in age from 70 to 75 and showed both retinal and peripheral sclerosis. The basal blood pressure readings ranged from 176/86 to 214/120. In five of these subjects, prolonged iontophoresis reduced the systolic blood pressure from 30 to 70 mm. of mercury, and the diastolic pressure from 10 to 30 mm. of mercury, so that both the systolic and diastolic readings reached normal or approximately normal levels in three cases. In the other two cases, the blood pressure was significantly reduced but not to normal. As in the previous group of subjects, the pressure remained at minimum levels as long as the current was applied and returned to or close to their original readings within a short time after the current was discontinued.



Of the other three cases, the reduction in pressure was as follows: Two of these subjects showed an interesting phenomenon—although the blood pressure fell close to normal levels at times, wide fluctuations occurred, so that high readings alternated with the minimum readings. In the third case, a negligible fall in blood pressure occurred.

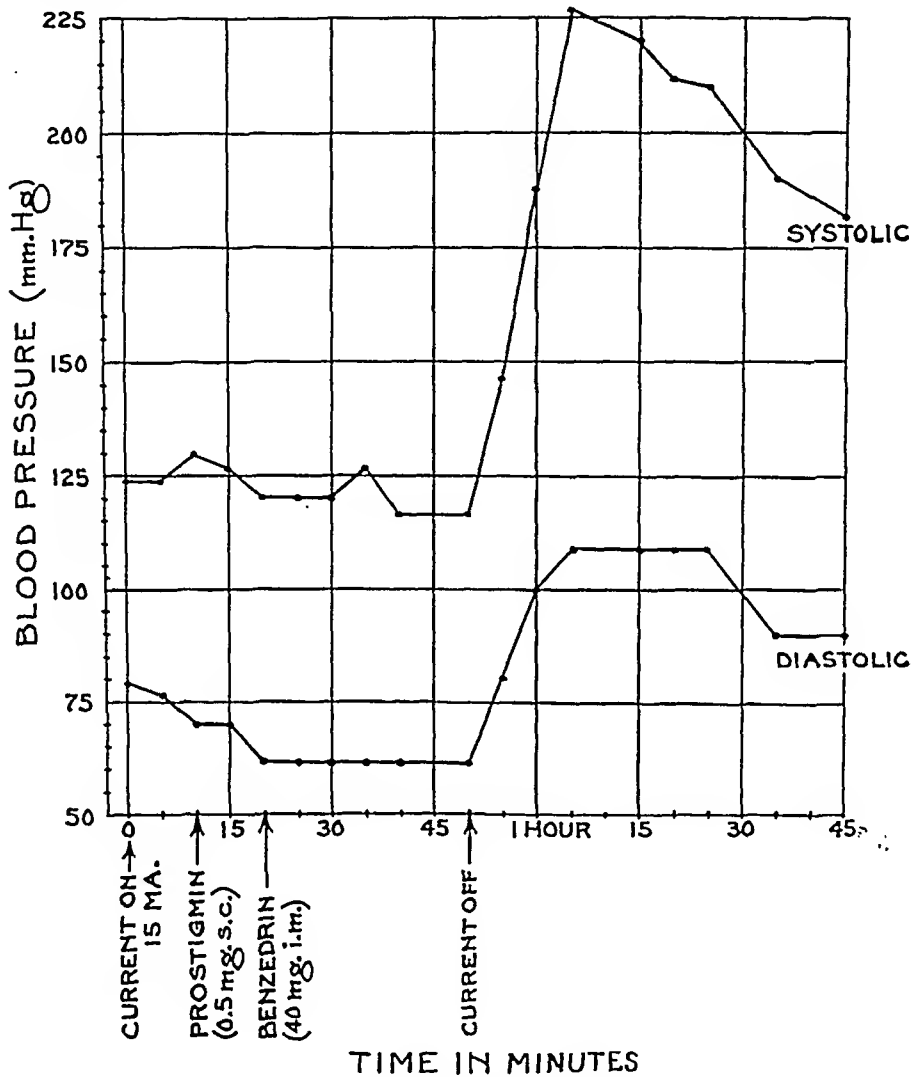


CHART 2 (Case G. T.): The counteracting effect of mecholyl iontophoresis preceded by prostigmin on benzedrine hypertension. The blood pressure remained unchanged for 30 minutes after the benzedrine injection, then quickly rose when the iontophoresis was discontinued.

The pulse rate in four of the eight cases showed either slight or insignificant changes. When the blood pressure had returned to the original level following the cessation of the iontophoresis, a significant fall in pulse rate occurred in four cases. Throughout the experiments the pulse showed no unusual rhythm or change in quality.

No correlation could be made between the state of the peripheral vessels

TABLE II  
The Effect of Mecholyl Iontophoresis on Senile Hypertension  
(8 Cases)

Case	Before Iontophoresis		Period of Iontophoresis			After Iontophoresis	
	Initial		Ht. of ABC* Reaction			Final	
	B.P.	Pulse	Minimum B.P.	Time†	Pulse	B.P.	Pulse
P. F.....	184/90	76	146/70	45 min.	80	172/80	72
P. W.....	194/96	80	174/106 148/88	—	88	190/118	68
A. W.....	214/120	68	184/110	10 "	68	220/126	68
H. R.....	190/110	60	186/100 140/80	—	72	200/110	60
D. S.....	200/110	104	158/80	38 "	104	196/116	96
E. M.....	176/86	60	144/70 110/62	43 "	64	178/90	60
J. B.....	196/106	72	142/88 126/76	45 "	68	200/110	68
A. S.....	210/108	60	200/108	—	72	240/120	76 <sup>2</sup>

\* Acetyl-beta-methylcholine chloride (mecholyl).

† Length of time normal blood pressure maintained.

and the fall in blood pressure. For example, one subject, with very hard and beaded radial vessels, showed an ideal response to the iontophoresis. In two cases, in which a marked blood pressure response occurred, the radial arteries, which felt thick to the fingers before the experiment, felt normal when the blood pressure reached a non-hypertensive level.

No evidence of any special discomfort or untoward signs occurred in any of the eight subjects; flush of the face and sometimes of the chest, with mild sweating, occurred in every case. Increased desire to urinate and audible intestinal peristalsis were present in the majority of the subjects.

3. *The effect of mecholyl iontophoresis preceded by the administration of prostigmin* (table 3, chart 4): Four senile hypertensives, three of whom had had an unsatisfactory fall in blood pressure with mecholyl iontophoresis alone and three other senile subjects were given subcutaneous injections of prostigmin (0.5 mg.) 5 to 15 minutes prior to the mecholyl iontophoresis. Prostigmin was administered because it is a marked synergist to mecholyl in modifying the autonomic functions of the body, including the sweat production, the regulation of blood pressure, the gastric secretion and the bladder tonus. The three subjects who responded unsatisfactorily to the administration of mecholyl iontophoresis alone and one other subject will be considered briefly:

(1) *Case H. R.*: This patient had a basal blood pressure of 210/110. Prostigmin (0.5 mg. s.c.) by itself was without effect, but followed by

mecholyt iontophoresis produced a gradual fall in 15 minutes to 140/70. These readings remained approximately stationary for 15 minutes, when the current was turned off to allow the patient to urinate. Following this, the blood pressure returned to a level of 210/105. Renewal of the iontophoresis caused a fall in blood pressure to 178/90 within 15 minutes. At this point the current was discontinued because of the patient's marked restlessness. In a previous control experiment, the same patient had been given iontophoresis without prostigmin and showed a fall in blood pressure

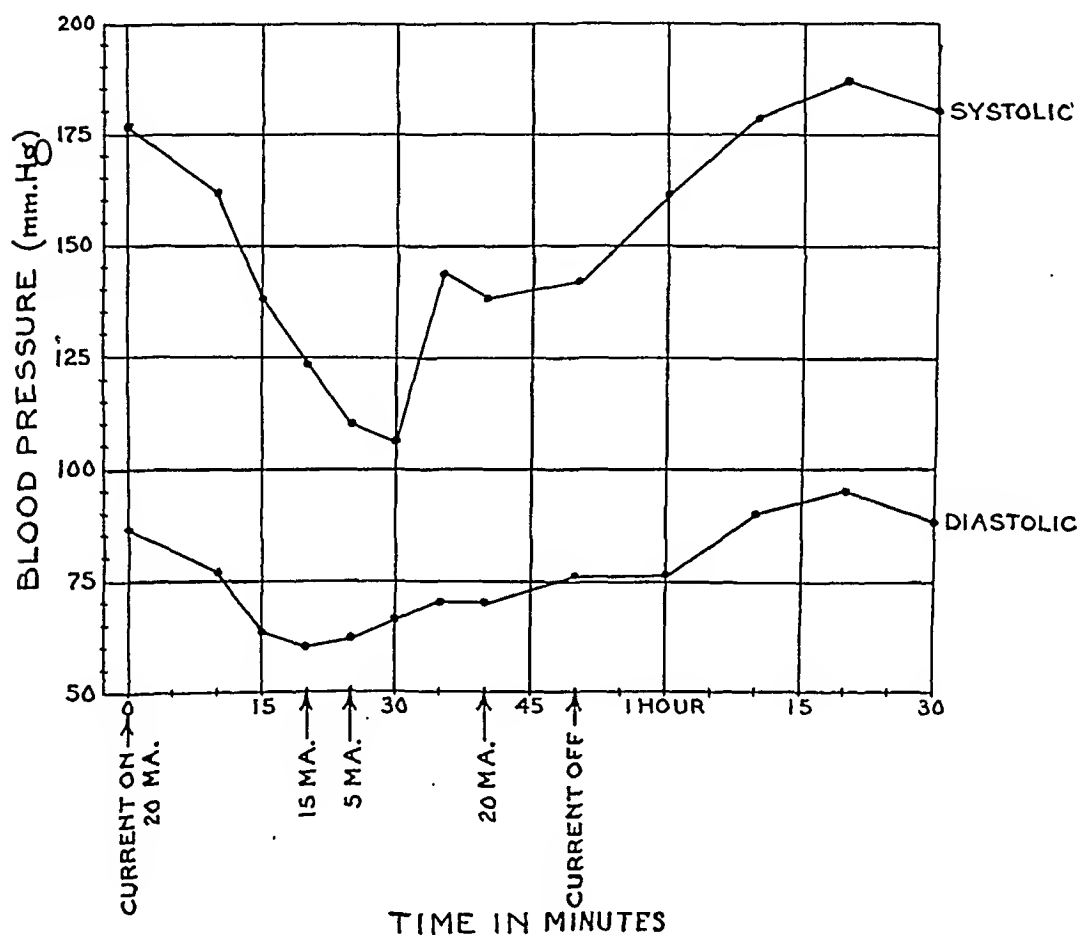


CHART 3 (Case E. M.): The effect of mecholyt iontophoresis on senile hypertension. The blood pressure was kept at a non-hypertensive level for about 43 minutes and returned to its initial high level after the current was discontinued.

from 190/110 to 140/80. These changes, however, could not be maintained; there was an alternation of a fall and rise between 140/80 and 186/100 during the iontophoresis.

(2) *Case P. W.*: This subject had very hard, tortuous radial vessels. When mecholyt alone was introduced by iontophoresis, there was a fall in blood pressure from the original reading of 194/96 to 148/88, the reduction being intermittent and ranging between the latter reading and 174/106.

When prostigmin was given subcutaneously, followed by iontophoresis, the blood pressure fell from 174/104 to 136/78 within 8 minutes, rose to 148/80 and remained at this level for 43 minutes.

(3) *Case A. S.* (Chart 4): By iontophoresis with mecholyl alone a negligible drop in blood pressure, from 210/108 to 200/108, occurred, using up 32 milliamperes of current over a period of 43 minutes. Sweating and flushing of the face occurred, showing that the drug was being introduced

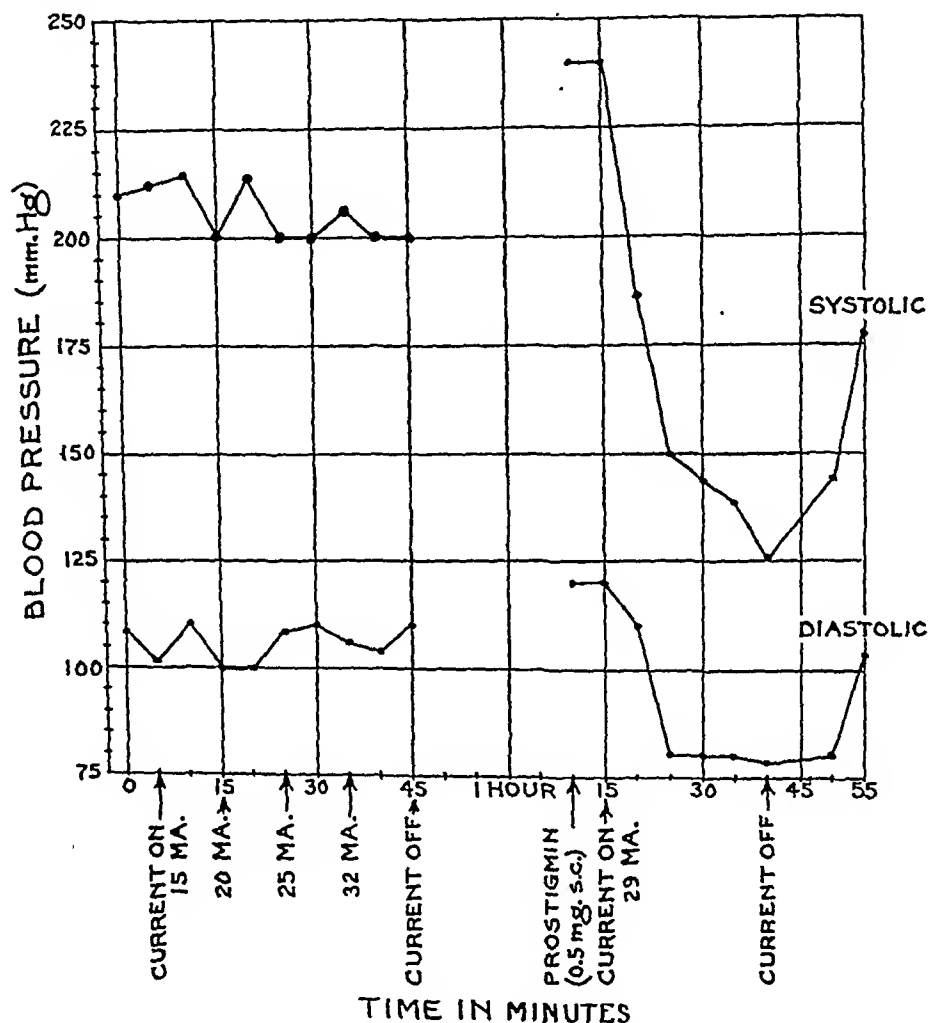


CHART 4 (Case A. S.): The effect of mecholyl iontophoresis on senile hypertension. Iontophoresis alone was ineffective, but when combined with prostigmin the blood pressure fell to a normal level where it remained until the current was discontinued.

in "physiological" amounts. Upon cessation of the iontophoresis, the blood pressure rose to 240/120 within the subsequent 25 minutes. At the end of this period, prostigmin (0.5 mg. s.c.) was administered and mecholyl by iontophoresis again given 5 minutes later. The blood pressure now fell steadily to 126/76 during the ensuing 20 minutes, with a current milliamperage of 20. Upon cessation of the current, the blood pressure quickly rose to 180/104. In the course of the iontophoresis, the patient urinated

twice, passing on one occasion 500 e.c., and on the other 300 e.c. The radial arteries, which seemed to be thick and hard at the beginning of the experiment, felt normal when the blood pressure was at its minimum.

(4) *Case J. B.*: This patient also showed a more satisfactory reduction in blood pressure when mecholyl iontophoresis was preceded by prostigmin than when mecholyl iontophoresis was employed alone. With the combination of drugs, he showed a fall in blood pressure from 196/104 to 110/64 within 12 minutes following the introduction of mecholyl by iontophoresis. Only 8 milliamperes of current were required to obtain this reaction. The minimum blood pressure was maintained at approximately the same level for 30 minutes, when the experiment was discontinued because of the patient's desire to defecate. Throughout the period of mecholyl iontophoresis the pulse remained at the rate of 60 and continued strong and regular. Twelve minutes after the current had been discontinued, the blood pressure returned to a level of 210/100. During the time the blood pressure was at its minimum, the radial vessels, which were moderately thickened originally, became soft. In a previous experiment, the same patient had been given mecholyl iontophoresis alone with a current of 25 milliamperes, as a result of which the blood pressure showed a satisfactory reduction, namely, from 196/106 to 126/76. There were fluctuations ranging between this latter level and 142/88 for a period of 45 minutes, at which time the current was discontinued.

The four other senile hypertensives, who received injections of prostigmin (0.5 mg. s.c.) preceding mecholyl by iontophoresis, showed very satisfactory reductions in blood pressure which were maintained as long as the current was continued (table 3).

TABLE III

The Effect of Mecholyl Iontophoresis on Senile Hypertension when Preceded by the Administration of Prostigmin (0.5 mg. s.c.)  
(7 Cases)

Case	Before Iontophoresis		Period of Iontophoresis			After Iontophoresis	
	Initial		Ht. of ABC* Reaction			Final	
	B.P.	Pulse	Minimum B.P.	Time†	Pulse	B.P.	Pulse
J. P.....	178/108	108	110/70	47 min.	92	168/112	76
J. P.....	166/106	80	122/74	40 "	80	172/104	64
H. R.....	210/110	60	140/70	25 "	72	210/105	52
P. W.....	174/104	80	136/78	43 "	88	174/100	72
A. S.....	240/120	64	126/76	28 "	60	180/104	60
J. B.....	196/104	68	110/64	30 "	60	210/100	56
E. McC..	178/90	64	138/70	18 "	72	230/110	58

\* Acetyl-beta-methylcholine chloride (mecholyl).

† Length of time normal blood pressure maintained.

## COMMENTS

It is probable that the mechanism by which benzedrine sulfate causes a hypertension is relatively simple compared to the mechanism by which essential or senile hypertension is brought about. The ability of acetyl-beta-methylcholine chloride, introduced by the method of iontophoresis, to overcome the vasoconstricting action of benzedrine, and thus produce a fall in the elevated blood pressure as long as the drug continues to be absorbed, is uniformly seen in the experiments noted herein. On the other hand, by mecholyl iontophoresis alone it is often difficult to lower the hypertension of senile subjects to normal levels. The failure in the latter cases may be due to the incapacity for dilatation of the arteries and arterioles and perhaps to the presence of high amounts of cholinesterase in the body, or to both causes. From the present experiments, no definite aid in explaining the failures is obtained from the state of the radial vessels, for satisfactory reductions in blood pressure occurred in instances in which the peripheral vessels were very tortuous or hard.

The injection of prostigmin preceding mecholyl iontophoresis definitely enhances the effect of the latter drug, as shown by the effect of both drugs on the seven senile hypertensives. Whether this synergism is accomplished by the destruction of the cholinesterase in the tissues, thus rendering the mecholyl more effective, or whether the prostigmin acts in some other manner is not known. In those cases in which the combination of prostigmin and mecholyl iontophoresis failed to effect a satisfactory reduction in blood pressure, there may have been too many arterioles so damaged as to be incapable of dilatation.

## SUMMARY AND CONCLUSIONS

1. In 10 young dementia praecox subjects, the hypertension produced by benzedrine sulfate was markedly reduced to normal or close to normal levels for periods varying from 30 to 90 minutes, that is, as long as the drug was allowed to be absorbed.

2. In three of eight senile hypertensives, the blood pressure was markedly reduced to normal or close to normal levels for varying periods of time.

3. In all of seven senile hypertensives, the administration of prostigmin prior to the mecholyl iontophoresis produced a reduction in blood pressure to normal levels. Three of these patients had failed to respond satisfactorily to iontophoresis alone. This suggests the possibility of a "hyperesterasia" which may play an important rôle in the production of hypertension.

4. No untoward effects were noted during the mecholyl iontophoresis. The rate of absorption of the drug is readily controlled by regulating the milliamperage, so that the blood pressure may be very gradually lowered. Only slight discomfort, consisting of flushing, mild sweat, slightly increased intestinal peristalsis, and desire to urinate are produced by the method.

The mecholyl used in these experiments was generously supplied by Merck & Co., the benzedrine sulfate by the Smith, Kline & French Laboratories, and the prostigmin by Hoffmann-LaRoche, Inc.

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## LOW CHEST AND UPPER ABDOMINAL PAIN \*

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SEVERE pain in the lower chest and upper abdomen is a symptom common to many affections involving several different systems of the body. Cardiovascular disease, respiratory disease, lesions in the upper gastrointestinal tract as well as certain lesions of the central nervous system may frequently produce pain in the upper abdomen or lower chest or both. Thus pain in the lower chest may be due to disease of the heart, lungs or pleura on the one hand, or it may be caused by gastrointestinal lesions alone. Likewise upper abdominal pain may be due to disease located either below or above the diaphragm. This state of affairs naturally leads to confusion and error in diagnosis but with treatment varying radically according to the origin of this type pain the importance of accurate diagnosis is apparent. With this in mind some of the more common causes of low chest and upper abdominal pain will be discussed together with a few illustrative case reports.

Of the cardiovascular affections, coronary disease ranks first in the production of low chest or upper abdominal pain. Acute coronary occlusion is the most severe if not the most frequent manifestation of coronary disease.<sup>1</sup> An acute coronary occlusion is typically ushered in by persistent severe pain beneath the sternum, usually radiating to the shoulder girdle and often down one or both arms. However, this radiation may be downward into the epigastrium or over to the liver and gall-bladder area; or occasionally into the lumbar back. Again, in less typical attacks the severest pain may be localized beneath the tip of the ensiform while in some cases nausea and vomiting together with epigastric fullness and discomfort are more pronounced than any chest pain. Particularly in these atypical cases it is the accompanying history, signs and symptoms that may lead to a correct diagnosis.

Such a case is that of a priest, 78 years of age, who had been hospitalized for some months following an amputation of his right leg for diabetic gangrene. He had made a complete postoperative convalescence but because of his age, his diabetes and the coincident generalized arteriosclerotic changes, had remained in the hospital to receive general diabetic care. One morning he complained of sudden epigastric distress with mild nausea. This same ill feeling had been noted intermittently and quite irregularly for a week or ten days prior. However, this attack was much more severe and was accompanied by a feeling of marked prostration, mild sweating and an immediate irregularity of the pulse. Several hours later he was much more comfortable but still unusually prostrated and his pulse remained irregular and somewhat faster than his average. On the following day he was better but still ill at ease, weak and somewhat apprehensive. Blood pressure at this time was 102 mm. of Hg systolic and 85 diastolic, as contrasted with his average of 126/80. Pulse now slowed to 70-80 per minute but still quite irregular. The following day a degree or two of fever was noted and a leukocyte count showed 11,500 cells. The fever and

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the leukocytosis remained another two days and then gradually came down to normal. During this time there was nothing remarkable to be heard on auscultation over the heart, except the irregularity. This persisted until a 2 to 1 block was apparent and finally a complete block with heart and pulse rate of 26 to 29. This latter was short-lived, however, and quickly a 2 to 1 rate was resumed. Electrocardiographic studies showed typical evidence of myocardial infarction and follow-up electrocardiograms were continued over a period of months until finally a complete return to normal was noted. Clinical recovery of course was apparent some time before this.

This case report illustrates the atypical variety of acute coronary occlusion in which diagnosis is based on observation of factors other than pain alone.

However well known the symptoms of a typical occlusion, it may be proper to briefly review them. Besides the pain which is usually most severe and unrelenting, the patient so affected is quite apprehensive, apt to be restless, changing position, moving from chair to bed and around the room. His skin is pale and sweaty such as is seen in minor degree of shock. Pulse rate is increased. Not infrequently some irregularity in rhythm may be noted. Dyspnea is present; it is usually of moderate degree only. Likewise slight cyanosis may be present. Dyspnea and cyanosis are ordinarily not marked but form a rough index of the efficiency of the circulatory apparatus. If myocardial damage has been severe, dyspnea and cyanosis will be more prominent. In an occasional case dyspnea may be the most prominent symptom from the beginning. Physical examination during the attack is usually not diagnostic of itself but may add considerable support for or against the presence of thrombosis in the given case. Blood pressure falls at first to below average for the individual, then gradually returns to normal after the acute phase of the attack has passed. Temperature early is normal or sub-normal but after an interval of a day or two a low grade fever develops usually not more than 101° or 101.5° F. The heart may be found to be normal in size and position and free of murmurs or occasionally some enlargement may be detected with or without a mitral or aortic murmur. Rigidity of the upper abdominal muscles with some accompanying tenderness may be present. This is confusing only if the other accompanying symptoms and physical signs are lost track of. With the fever a leukocytosis develops, usually from 12,000 to 20,000. Occasionally a pericardial friction rub may also be detected at this time, some two to four days after the onset. This pericardial friction rub does not occur commonly but when present constitutes the most certain diagnostic sign that may be elicited by physical examination. Experienced clinicians generally recognize a slightly muffled quality or indistinctness of the heart sounds during an attack of acute occlusion. The heart sounds seem distant and are not as clear-cut as normal. The history in these cases of coronary thrombosis usually reveals the onset of the attack while the individual was at rest. The patient is nearly always in the arteriosclerotic decades of life and a past history of hypertension or

of anginal attacks lends considerable evidence in favor of a thrombosis. Another noteworthy feature in these cases is the marked prostration and ready fatigue which follow the attack and which persist for weeks or months. Finally an electrocardiogram made usually the sixth or seventh day after the onset of the attack will show changes typical of the condition. If serial electrocardiograms are made their diagnostic importance is increased.<sup>2</sup>

First cousin to coronary thrombosis in symptoms and etiology is angina pectoris, since both affections are due to interference with the coronary circulation and to the presence of some degree of coronary sclerosis.<sup>3</sup> The anginal pain may be at first indistinguishable from that of actual thrombosis; but in the former the interference with coronary circulation is temporary while in the latter it is permanent, and the clinical course varies accordingly. Anginal pain is a matter of seconds or minutes while that of thrombosis is of minutes, hours or even days. Anginal attacks are precipitated by greater than average exertion, either physical or emotional, while attacks of thrombosis are not so directly related to either. Of course anginal attacks may and often do, precede an actual occlusion but in such a case both the patient and the doctor usually realize that there has been a more serious, more prolonged and more disastrous turn in events. The patient with a typical anginal attack is nearly always seized while in the midst of some physical or emotional or nervous activity. During the attack he remains peculiarly and strikingly still wherever he may be at the time of the onset. He is usually quite apprehensive. Physical examination shows normal pulse, blood pressure and heart sounds. The attack is soon over and fever and leukocytosis do not follow.

Coronary disease is responsible for still another group of cases presenting low chest or upper abdominal pain as their chief symptom. This is the group of early coronary sclerosis with neither frank anginal nor thrombotic manifestations but who complain of discomfort after eating or after moderate exercise or both.<sup>4</sup> This group is perhaps of more importance relatively than any other because it includes those cases in which the diagnosis is most often missed and in which an accurate diagnosis at this stage would be of greatest benefit to the patient. These patients are regularly treated for indigestion and all too often die of an acute coronary occlusion or sudden myocardial failure and are listed by our daily press as victims of "acute indigestion." Patients in this group are in the arteriosclerotic age, usually past 50, often past 60 years of age. Physical and laboratory examination are productive of little or nothing out of the normal. It is the careful history that discloses the true nature of the case. Distress, fullness, epigastric discomfort, aerophagia and belching are the symptoms that lead these folk to seek relief from indigestion but close questioning shows that these symptoms develop only when some extra load is thrown on the circulatory apparatus, typically when some even quite moderate exertion is attempted soon after a meal. Usually the symptoms are more

marked if fatigue is present and therefore it is commonly the evening meal that produces the most distress, also because the evening meal may be the heaviest. However, symptoms do not necessarily immediately follow a meal.

Such a case was M. S., a man past 60, who complained of a distress which was localized definitely in the epigastrium. This distress was described as a feeling of heaviness which appeared at fairly regular intervals, particularly after the midday meal. Because of the location and periodicity of the distress a diagnosis of duodenal ulcer had been made. Upon questioning it was learned that the discomfort was seldom experienced except after his lunch. Further it was found that this patient was in the habit of walking to his office about one hour after his lunch and that it was during this time that the distress was usually noticed. He had already observed that the pain promptly subsided after he had reached his office and that he might obtain relief by resting on the way. Still further questioning showed that this man could literally eat peanuts, popcorn and crackerjack without digestive distress but that his symptoms developed only when the extra circulatory load of exercise was added to that of digestion.

There is great variation in the symptoms presented in this group of early coronary sclerosis but the significant facts which may be brought out by careful questioning are: first, that ordinarily speaking digestion per se is good; second, that symptoms appear only when a load of some kind is placed on the circulatory system; and third, that simple rest has been found most effective in relieving the symptoms.

Closely allied to these coronary types is a group of patients in whom upper abdominal pain results from interference with circulation in the upper abdominal vessels themselves.<sup>5</sup> These are variously classified as cases of intermittent claudication and abdominal angina.<sup>6</sup> They are recognized by the absence of other organic disease which might explain the pain present and by the pertinent history that they occur only when there is an increase in the circulatory load of these vessels, that is after meals and especially after heavy meals.<sup>7</sup> Fatigue is a frequent predisposing factor. Their occurrence may be intermittent or rhythmic, in the latter case suggesting strongly the presence of gastrointestinal disease. They occur almost without exception in the latter decades of life when arteriosclerosis becomes manifest. However, an occasional case of pure vascular spasm in much younger individuals has been reported. In passing it is noteworthy that the condition of the peripheral arteries is seldom an index to the absence or presence of atheromatous and sclerotic changes in the heart and viscera.

Heart failure from whatever cause, if of relatively sudden onset may produce severe upper abdominal pain with nausea and vomiting.<sup>8</sup> Likewise acute pericarditis may commonly be ushered in with severe low chest and upper abdominal pain accompanied by nausea and vomiting, tenderness and rigidity.<sup>9</sup> The differentiation in this latter condition is made by first suspecting the true condition present, by hearing a pericardial friction rub and later by the presence of pericardial effusion.

The next large group of cases presenting upper abdominal and often

low chest pain as their prime symptoms are those due to disease of the gastrointestinal tract.

The esophagus is a rather silent uncomplaining organ and yet it is not infrequently the offender in pain beneath the sternum. For some reason it is rarely thought of in our consideration of possible causes of this type of distress and for this very reason diagnoses may be missed.<sup>10</sup> Inflammation, ulceration, diverticula, tumors and simple spasm of the esophagus occur with regularity and each may produce pain. The cardinal symptoms in esophageal disease are distress beneath the sternum, and difficulty in swallowing. The distress may be only a feeling of pressure or of constriction, or may be actually painful as a burning sensation, or may be more severe as a boring or steady pain. The significant point is that it is always aggravated by the act of swallowing. When organic disease is present, such as ulcer or tumor, coarse food or a large bolus of food will produce the most discomfort; while in simple spasm iced drinks usually cause the most discomfort. Warm, demulcent, soft foods usually are soothing and relieve the distress to a greater or less degree regardless of cause. The difficulty in swallowing, or dysphagia, is often described as a feeling as though food or liquid stopped or lodged at a certain area and there is a perceptible time interval before it passed into the stomach. Often several swallows are necessary to move the bolus through. Sometimes it may be regurgitated if the obstruction is great.

Last month a woman was seen suffering with a burning pain beneath the lower sternum, continuous but much aggravated by the swallowing of food or liquid. She was in a hospital following delivery of an infant just four days before. Because of the severity of the pain, its location, and its duration the intern on duty suggested that she had a coronary thrombosis. However, upon questioning it was found that her anesthetic had been unusually prolonged at the time of delivery and that this substernal discomfort was noted almost as soon as she had regained consciousness. Because of the typical character of her distress and the absence of any other signs or symptoms, a diagnosis was readily made of post-anesthetic esophagitis. This was borne out by the rapid disappearance of her pain when she was placed on a diet of gruels and other soft, warm, demulcent food exclusively.

Diaphragmatic hernia is another cause of pain in the epigastrium and lower chest and one which is difficult to discover.<sup>11</sup> These herniae may occur at any age and give symptoms of mild dysphagia, low chest discomfort, pressure, sometimes burning usually following a meal. All symptoms are aggravated by lying down soon after eating and are relieved by assuming the upright position. Many of these cases have chronic blood loss from petechial hemorrhage or from actual ulceration at the area of herniation and on examination are found to have a marked hypochromic type anemia. The diagnosis in these cases is suspected from the history but proof of their existence depends on their recognition during roentgen-ray study at which time the patient's head and shoulders are tipped down so that a marked Trendelenburg position is assumed.

Ulceration of the gastric mucosa close to the cardia, like ulcers at or just

above the cardia in the gullet, usually produces pain high in the epigastrium or beneath the lower sternum or xiphoid. Although the symptoms are typically ulcer-like yet the difficulty in diagnosis is the fact that this area in the stomach is the most difficult of all to visualize either by roentgen-ray or by gastroscope. The chronicity of the pain, its periodicity and its location should make one suspect the presence of an ulcer in these cases. Another significant feature here is the effect of position on the discomfort. Patients with ulcers high along the lesser curvature are usually much more comfortable in an upright position than in a reclining one. One such patient had gone to the trouble of building a back rest in his bed so that even in his sleep he would remain semi-upright. Ulcers in this location, as well as those close to the pylorus, require constant observation because of the high incidence of carcinoma. Simple uncomplicated peptic ulcers do not give sharp or well localized pain. However, when they begin to penetrate deeper into the wall or when they perforate, with accompanying peritoneal irritation, then the character of pain changes, becoming much sharper, more constant, better localized and often radiating according to their location, up or down or to one side. Those with radiation of pain into the lower chest sometimes present problems of diagnosis coming within the scope of this paper.<sup>12</sup> They are to be recognized because of the past history of more typical ulcer symptoms and the presence of well localized tenderness and muscle rigidity which accompanies penetration or perforation. Direct visualization of the esophagus and stomach, together with the older more generally used methods of examination should demonstrate fully 95 per cent of all lesions occurring in these organs.

However, the gastrointestinal lesions which cause the greatest confusion in their diagnosis are those acute episodes associated with perforation of an abdominal viscus, an acute biliary colic, or an acute pancreatitis. When Paul White of Boston<sup>13</sup> and the late Harlow Brooks of New York,<sup>9</sup> two of the country's outstanding internists, freely admit making diagnostic errors in these cases, it is easy to see how difficult this and similar differentiation may be at times. However, again, the methodical history and the careful follow-up are usually the deciding factors in an accurate diagnosis.

Cases of renal colic are notably difficult to distinguish from biliary colic, and either may at times cause pain referred more to the mid-epigastrium or lower chest.<sup>14</sup>

An instructive case to me was that of Mrs. N. G. W. who was seized with sudden severe epigastric pain an hour after her breakfast. This pain was constant and involved the lower third of the substernal area with radiation to the shoulders. The pain lasted two hours, was not appreciably relieved by a hypodermic of  $\frac{1}{4}$  grain of morphine but finally vomiting occurred and following emesis there was marked relief. The patient was 57 years of age. Blood pressure at the time of her attack was 150 systolic and 72 diastolic. Examination showed an anxious facies, cool damp skin, pulse 92, regular and good volume. Some dyspnea was apparent. There was moderate but definite tenderness over the upper belly generally, most marked in the epigastrium but without muscle spasm. Examination of the heart showed it to be

normal in size and position but with a roughening of the first sound over the aortic area without significant change in the second sound. My impression recorded at the time was "acute coronary occlusion." The following day she was more comfortable but still complained of chest, epigastric and shoulder pain. The upper abdomen was still sensitive to pressure. Blood pressure 140/70. The following day, 48 hours after the initial attack, she complained again of some increased pain low under the sternum and in the epigastrium. She had felt chilly and her temperature at this time was 100° F. The day following she was more comfortable, her temperature was normal and her blood pressure 100/55. I felt pretty secure in my diagnosis of an occlusion and awaited the time for an electrocardiogram to establish the diagnosis beyond question. This was made and to my surprise and chagrin proved to be entirely normal in every respect. At about this time she again experienced an exacerbation of her acute pain and again had a slight fever. This continued for several days and by this time even I was convinced that her difficulty was not due to a coronary accident. She improved but still had intermittent attacks of pain and some fever. The past history of this case included a cholecystectomy one year before when a gall-bladder containing stones had been removed, with an unusually gratifying postoperative recovery. She had experienced a good deal of bladder irritability in the past, otherwise her past history seemed irrelevant. A month had passed by this time since her original acute seizure and during this time her bladder symptoms became more pronounced. Urine examination had been made repeatedly and always showed a trace of albumin and some increase in leukocytes with occasionally clumping but no red blood cells. With the increase in her urinary symptoms attention was directed to a possible pyelitis as responsible for her present illness and with this in mind she was hospitalized and a complete genito-urinary survey done by a competent urologist. He reported a trigonitis and a positive streptococcus culture from the left kidney, and otherwise negative findings. While we were thus struggling, trying to eradicate all urinary tract infection and believing that at last we had found a possible basis for her symptoms, she disappointed all of us again by having an acute episode of severe epigastric pain, with nausea and vomiting. This time, however, tenderness was much more marked in the right hypochondrium. After surgical consultation, laparotomy was decided upon and the following day a stone was removed which had partially obstructed the common bile duct. The obstruction had not been sufficient to produce clinical jaundice. This was a year ago and she has remained entirely free from symptoms since.

This case is an excellent example of diagnostic error committed in the face of low chest and high abdominal pain and was the basis for the present inquiry into the subject.

Acute pancreatitis is always difficult to diagnose. These cases are generally operated upon for intestinal obstruction or acute perforation of an ulcer. This mistake is of no great moment as the diagnosis is quickly corrected when the laparotomy is done. However, operating upon cases of acute coronary thrombosis is bad. Just as bad—probably worse—is failing to operate in the presence of an acute intra-abdominal lesion, believing the symptoms to be coronary in origin. Certain of these mistakes are unavoidable but many need not be made if the cardinal signs and symptoms in each case together with the past history are carefully considered.<sup>15</sup>

Disease of the lungs and pleura may result in low chest or high abdominal pain and may present difficulty in diagnosis. Basal pneumonia in children is often mistaken for intra-abdominal disease. Likewise pleurisy

especially with diaphragmatic involvement at any age.<sup>16</sup> Cases of spontaneous pneumothorax have been reported in which abdominal pain was so great that laparotomy was done.<sup>17</sup> A careful history and careful physical examination should suffice to make a correct diagnosis in most of these instances. There is one type of pulmonary accident, however, that may be very difficult to differentiate and this is sudden pulmonary infarction. These cases may begin with a sudden, terrific pain in the lower chest, or substernal area, and may have radiation of pain into the abdomen, shoulders and arms. The pain is often indistinguishable from that of acute myocardial infarction from a coronary occlusion. However, the dyspnea is usually much more pronounced and often cyanosis is a feature. The differentiation may be made by roentgen-ray examination of the chest and by electrocardiography. However, at the time of the attack the significant factor is in the history of a recent fracture, injury or operation. Postoperative patients rarely have coronary occlusion but not infrequently have pulmonary infarction. Likewise following a fracture a pulmonary infarction may occur.

Such a case was that of Mr. F. C. E., an engineer 49 years of age, who was seen early one morning last November suffering from an attack of severe low chest and substernal pain. This attack had begun during the night. The pain was the most severe the patient had ever experienced and as his history revealed that five years before he had had a gall-bladder removed because of repeated attacks of gall stone colic and that three years before he had passed a stone from his bladder following a severe attack of kidney colic, I thought he must know when he said he had experienced severe pain but that this attack easily topped them all. This pain radiated from his chest to his neck, to his left shoulder, and down the left arm to the wrist. He appeared to be critically ill. His facies was anxious, skin pallid, grayish, and covered with sweat, dyspnea most marked and some cyanosis was noted of the lips and nail beds. His temperature was 97.6°, pulse 100, regular, small volume. Blood pressure 110 systolic and 70 diastolic.

The patient was at this time wearing a cast on his left foot and leg because of a Potts fracture suffered three weeks before. Within the next few hours he suffered two attacks of severe dyspnea and cyanosis but finally pulled out of each. The following day he was somewhat improved but had developed a temperature of 100.2° F. At the end of four days his temperature had returned to normal and he was feeling quite comfortable. An electrocardiogram made two days later was negative and a few days thereafter he was removed to the hospital where a roentgen-ray of the chest showed a small area of opacity in lower lobe of left lung which was interpreted as a resolving infarct in that area. While still in the hospital and exactly two weeks after his initial attack he was again seized with severe pain, dyspnea, and cyanosis; this time, however, the pain was in the lower right chest. Roentgen-ray of the chest at this time showed complete consolidation of the right lower lobe with some free fluid present. The area in the left chest was much decreased. Chest roentgen-ray made at the end of one month showed tenting of the right diaphragm, the result of pleuro-diaphragmatic adhesions. The lung fields, however, were entirely clear.

This is an interesting case of pulmonary infarction on the left side occurring three weeks after a Potts fracture, to be followed two weeks later by a second pulmonary infarct, this time on the right side. Hemoptysis is

sometimes present in these large infarcts but was absent in this case. The chief differential point to my mind was the history of Potts fracture three weeks prior, plus a negative history of prior cardiovascular symptoms, such as hypertension or anginal attacks. Final diagnosis depended on a negative electrocardiogram with positive roentgen-ray findings.

To complete our list of possible causes of low chest and high abdominal pain mention must be made of certain affections of the central nervous systems, more especially of the spinal cord or ganglia. I have seen a case of herpes zoster, or shingles, of the lower left chest being treated for coronary thrombosis. This mistake should not be made but the location and severity of the pain were such as to mislead the attending physician. Of course after the typical eruption appeared there was no possible doubt as to the diagnosis. Cord tumors in the low cervical or upper dorsal area may produce severe chest pain. Usually in these cases there is a definite radiation and symmetrical distribution of the pain together with areas of hyperesthesia or anesthesia that are more or less diagnostic. There are, however, cases of bony changes in the vertebrae with spinal irritation which are much more confusing. Here due to irritation of a spinal nerve on one side, there may be severe one-sided chest pain. In 1934 Nachlas<sup>18</sup> described a syndrome of pseudo-angina pectoris originating from demonstrable changes in the cervical spine. The distinguishing feature in these cases is that ordinarily a careful history reveals the nature of the pain as neuralgic and significantly much accentuated by certain movements of the neck, shoulders or arms, and also aggravated by walking or jarring. Often too this pain is definitely confined to the radiation of a specific spinal nerve. The shoulder girdle is primarily involved in most of these cases and a diagnosis at one time or another has been made of arthritis of the shoulder.<sup>19</sup> We have had one case of Paget's disease where chest pain was a prominent feature and here the pain was thought due to bony changes in the cervical vertebrae, with resulting nerve irritation. Mediastinal tumors may by pressure also produce spinal ganglia irritation with the same symptoms.

Even yet our list is far from complete. There are still other causes of low chest and upper abdominal pain—tabetic crises, lead poisoning, uremia, eclampsia, diabetic coma,<sup>20</sup> acute gastritis, mucous colitis, dissecting aortic aneurysm, carcinoma of bronchus and lungs, hyperthyroidism,<sup>22</sup> paroxysmal tachycardia, sensitivity to tobacco, tea or coffee<sup>23</sup> and marked anemia, are some causes mentioned in the literature. There are undoubtedly others. We have tried to limit our discussion to the more usual and the more often confused causes of pain in this area.

In conclusion sudden, severe pain in the lower chest and upper abdomen is a symptom common to many affections of several different systems of the body. Diagnosis in these cases is often difficult because the pain may be the same in all. Accurate differentiation must be based not so much on the pain itself as upon careful consideration in each case of the accompanying history, symptoms and physical signs.



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# THE CHEMICAL NATURE OF HEART FAILURE\*

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HEART failure in its commonest and simplest form represents an inadequacy in contraction of a critical number of individual heart muscle cells. Every clinician has witnessed the death of patients with evidences of complete myocardial insufficiency only to have pathologists offer nothing more than slight microscopic myocardial changes to account for the clinical picture. In such instances, we have hesitated to admit the histological abnormalities as full explanation of the complete insufficiency in myocardial function. On the other hand we have seen serious and extensive pathological processes demonstrated in the hearts of patients who during life have shown no evidence of primary heart failure. It has, therefore, been widely appreciated that anatomical findings in themselves often fail to show satisfactory correlation with the functional status of an organ.

Unwillingness to accept a purely structural basis for myocardial weakness has initiated research that has been directed toward the establishment of a more adequate concept of the disturbance in fundamental cellular physiology. In comparison with the tremendous amount of physiological data that have accumulated concerning the physical or mechanical response of the heart under various conditions, studies of the disorders of the cellular metabolism or biochemistry of the heart muscle cells have been relatively few and the available data are meagre. Within the last decade, however, considerably more attention has been accorded the chemical physiology of the heart. Derangement of the physicochemical processes concerned in cardiac muscular contraction has long been suspected.

Meakins,<sup>1</sup> in a paper in the *ANNALS OF INTERNAL MEDICINE* in 1932, directed attention to the newly established facts concerning phosphocreatine (Fiske and Subbarow<sup>2</sup>) or phosphagen (Eggletons<sup>3</sup>) in the skeletal muscle physiology and commented upon a possible analogy in heart muscle function. He, however, stressed the importance of cardiac glycogen and lactic acid formation as affected by oxygen deficiency and acidosis and other metabolic disturbances and related them to circulatory failure.

The important conditions known to lead to failure of the cardiac muscle to function properly, in the light of Meakins' investigations, were similar to those of Harrison<sup>4</sup> and the Vanderbilt group, namely oxygen want, insulin deficiency and a defect in cardiac glycogen metabolism. He discussed other related metabolic disorders as thyrotoxicosis and mentioned the newer concepts of muscle chemistry but confined his main thesis to glycogen

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metabolism, which subject he and his co-workers have investigated. Evans<sup>5</sup> and his group, and Cruickshank<sup>6</sup> and his associates, Himwich<sup>7</sup> and others have made further contributions to this phase of the subject.

Eppinger<sup>8</sup> and his school in 1927 demonstrated the increased lactic acid content in the peripheral blood in heart failure and held accountable for this an oxygen want in the skeletal muscles. The demand for oxygen in the periphery, Eppinger et al. concluded, would lead to an increased peripheral blood flow on the arterial side in spite of venous stasis and an increasing oxygen debt and thus would create a vicious circle. Jahn<sup>9</sup> suggested that the persistent flooding of the organism with lactic acid might contribute to the exhaustion of an otherwise damaged heart. Glycogen and lactic acid metabolism maintain a position of importance in heart muscle investigations in spite of the present interest in other substances. The intermediate products of carbohydrate metabolism are closely linked with phosphates; glycogen breakdown appears to yield hexosephosphates and these subsequently may be converted into lactic acid via the formation of various triose phosphates.

Lundsgaard's<sup>10</sup> observations that muscle poisoned with iodoacetic acid could contract without the formation of lactic acid called for modification of the Hill and Meyerhof theory which considered muscle action wholly dependent on glycogen and lactic acid metabolism. The most studied processes in energy liberation in muscle were thus relegated to a secondary position and the fact emphasized that the chemical energy of muscular contraction had to come from another source. Embden<sup>11</sup> and his co-workers had shown that at the end of contraction the reaction was normally alkaline and not acid. Embden had also observed that phosphates played a rôle in muscle cell metabolism.

The American workers, Fiske and Subbarow<sup>2</sup> discovered a labile "phosphocreatine," a K salt or compound of creatine and phosphoric acid, which they considered the primary constituent necessary for muscular contraction. The practically simultaneous independent report of the Eggletons<sup>3</sup> in England of a similar organic phosphate compound which they called "phosphagen," and later recognized to be identical with phosphocreatine, established the latter as the active principle of muscle cells. Both groups of workers found the compound to break down exothermically to supply the energy for muscle contraction.

Halogen acetic acid has been found to stop the anaerobically beating heart by striking at the change from phosphoglyceric to phosphopyruvic acid which is one of the steps in the anaerobic mechanism available for the supply of energy for resynthesis of creatine phosphoric acid. Glycogen is broken down to lactic acid which appears only at the end of contraction and contributes, according to Lehnartz,<sup>12</sup> Embden and Deuticke<sup>13</sup> and Lohmann and Meyerhof,<sup>14, 15</sup> the energy for the resynthesis of phosphocreatine under such circumstances. The combination or the intermediate product lactacidogen or hexosephosphate may act as a buffer.

Analogies between skeletal and cardiac muscle physiology have been drawn and are being gradually established. Clark and the Eggletons<sup>16</sup> early pointed out that the myocardium contains but one-tenth to, at the most, one-fourth, as much phosphocreatine as voluntary muscle. They considered the lower levels adequate in that the diastolic pause following each systole allowed sufficient time for resynthesis, and tetanization cannot occur. Vollmer<sup>17</sup> found phosphocreatine constituting 75 to 80 per cent of the total creatine at rest, but only 20 to 25 per cent at the end of contraction.

Other phosphate compounds as adenylic acid and hexosephosphate were found by Pohle<sup>18</sup> and also by Pollock, Flack, Essex and Bollman<sup>19</sup> to be present and active in heart muscle. In the breaking down of phosphocreatine, the phosphorus liberated is taken up by the adenylic acid to form adenosine triphosphoric acid; this reaction is reversed during the resynthesis of phosphocreatine. During the coincident carbohydrate metabolic cycle, there is an exchange of phosphorus between the hexose and triose phosphates on one hand, and adenylic and adenosine triphosphoric acids on the other. Lohmann has demonstrated adenylypyrophosphate and adenosine diphosphate in heart muscle. Cruickshank<sup>6</sup> states that adenylic acid is only abnormally present in heart muscle when synthesis of adenosine triphosphoric acid is incomplete. Under such conditions he states that the free adenylic acid or adenine would be deaminated to inosinic acid or hypoxanthine and ammonia. Incomplete phosphocreatine formation, a lack of prompt rephosphorylation of creatine, a depletion of glycogen reserves and an increase in orthophosphates, all might accompany progressive heart failure. In anoxic states or in the presence of inadequate oxygen supply theoretically the resynthesis of adenosine triphosphoric acid would lag behind the formation of lactic acid and creatine and ammonia would be formed and lost.

Clark, Eggleton and Eggleton<sup>16</sup> showed that the ratio of phosphocreatine to orthophosphate under favorable normal aerobic conditions was 0.6 for the frog's heart and 1.0 for the tortoise. Cruickshank<sup>6</sup> and his associates demonstrated a similar relationship for the mammalian heart and concluded that the phosphocreatine-orthophosphate ratio is an index of the physiological condition of the mammalian heart.

An index of phosphocreatine, the so-called total creatinine of muscle most of which is creatine, must be established. It is also apparent that, in addition, in order to obtain more complete chemical data in human and animal heart muscle in various functional states the amounts of phosphorus compounds must be determined.

The total phosphorus (Pt), includes a fraction that is soluble in 5 per cent trichloroacetic acid and an insoluble fraction. The acid soluble phosphorus (Pas) fraction, according to Lehnartz,<sup>12</sup> is made up of inorganic or orthophosphoric acid (Po), phosphocreatine, hexose phosphate, nucleotid phosphoric or adenylic acid as adenyly pyrophosphoric acid or adenosine-triphosphoric acid, and constitutes the "activity substances" of Embden.<sup>22</sup> The fraction not soluble is the residual phosphorus and consists, according

to Sorg<sup>29</sup> and Wassermeyer<sup>30</sup> of phosphatids or lipids. Cullen, Wilkins, and Harrison<sup>28</sup> found the total phosphorus to be low in the myocardium of a small series of patients who had died in congestive heart failure.

Sorg<sup>29</sup> has shown that the difference between the total phosphorus and the acid soluble phosphorus very closely approximates the lipid phosphorus (Plip), which is difficult to determine directly. Wassermeyer<sup>30</sup> has found that the total and acid soluble fraction did not change after the death of the muscle and could be studied in human autopsy material and followed a regular distribution in different parts of the dead heart. White,<sup>31</sup> Kutchera-Aichenberger<sup>32</sup> and Lehnartz<sup>12</sup> all considered the lipid phosphorus important since they found that heart muscle contained twice as much as did skeletal muscle in most animals. Kutchera-Aichenberger<sup>32</sup> found decreases in lipid phosphorus after experimental myocardial injury produced by chloroform and in human autopsy material from heart failure cases but Wassermeyer and Rohrbach<sup>33</sup> found no lipid changes in various types of experimentally induced myocardial damage.

According to Wassermeyer<sup>30</sup> human hearts show a regular decrease in these substances, particularly the lipoids, as the age advances toward 70 years. Coronary sclerosis in hearts was accompanied by a regular decrease in the total phosphates but also a drop in the lipoids. In a few decompensated hearts, there were no significant changes in the total phosphate but usually a definite lowering of the lipoids in the left ventricle.

The possible importance of this lipid fraction was further emphasized by theoretical considerations of the physicochemical possibilities, namely, the probable importance of lipid phosphates in the processes at the cell surfaces. The susceptibility of the lipid phosphates to changes brought about by calcium and indirectly by digitalis administration increases the desirability for further investigation of these substances.

#### A BIOCHEMICAL APPROACH TO THE PROBLEM OF HUMAN HEART FAILURE

We have, during the past ten years, directed studies in the fundamental chemical changes that accompany heart failure. At first, we were concerned with the part played by inorganic salts of calcium and potassium.<sup>20, 21</sup> With the gradual development and diffusion of the newer conceptions of phosphocreatine or phosphagen in muscle physiology, we began our investigations of the organic constituents of the heart muscle. We have analyzed the heart muscle of animals under various experimental conditions and of human autopsy material. Determinations of the total creatinine (practically all of which is creatine), of total and acid soluble phosphorus as well as of calcium and potassium were made.

The great technical difficulties in determining phosphocreatine in mammalian muscle and the impossibility of determining phosphocreatine in human heart muscle halted for some time progress in the matter of clinico-pathological biochemical studies. The suggestion of Pekelharing<sup>22</sup> carried

out by Constabel<sup>23</sup> and by Seecof, Linegar and Myers<sup>24</sup> and by Cowan<sup>25</sup> on the relation of the creatine content of human heart muscle to myocardial function gave great impetus to further research along this line. The acceptance of the total creatinine content of dead heart muscle as a probable index of the level of phosphocreatine in life afforded a means of attack of the problem. Instead of the labile phosphocreatine, we have, therefore, determined the total creatinine in our experimental and clinical material.

In the beginning, we undertook studies of blood and urine constituents, particularly total creatinine and creatine, in patients with acute coronary obstruction and myocardial infarction.<sup>26, 27</sup> We found a definitely abnormal creatinuria and a rise in the blood creatine levels beginning within a few hours after the onset of an attack and continuing for several days to a week depending perhaps upon the size of the infarct.

#### EXPERIMENTAL TOTAL CREATININE STUDIES

A series of dogs was sacrificed at varying periods of time after the occlusion of the blood supply to a section of the myocardium by tying of the anterior descending branch of the left coronary artery. We substantiated the finding of a sharp drop within the first few hours in the glycogen content of muscle from the infarcted areas. We also noted slightly delayed but striking loss of total creatinine, beginning after the fifth hour of infarction.<sup>27</sup>

The problem was then attacked further experimentally in various ways and chemical analyses of the heart muscle were carried out after the production of various types of experimental myocardial damage.

Another series<sup>34</sup> of rabbit hearts was isolated and perfused for six to eight hours in a modified Dawson-Gunn-Locke apparatus with warm oxygenated Ringer-Locke solution. The hearts in this series that were infarcted, by the lodgement in their coronary arteries of small particles from the perfusion fluid, showed the lowest total myocardial creatine values that we encountered. The uninfarcted hearts that were perfused to failure, which occurred at the end of six to eight hours, likewise presented very low creatine content. It was further shown that a fall in the pH due to lactic acid accumulation in the perfusate was accompanied by an added loss of creatine.

Further experimental attempts<sup>32</sup> to stay the dissipation of total creatinine were carried out. Some of the various amino acids that have been suggested as possible precursors of creatine, namely glycocoll, glyocyamine, arginine, alanine, glutamic acid, aspartic acid, methylguanidine, and creatine itself were added to the perfusate and the effects were noted. In our studies all amino acids with the possible exception of alanine and to a slight extent glycocoll, failed to maintain normal total creatinine values in the isolated heart. Alanine seemed to spare the creatine, and its effects as that of glycocoll, might be attributed to its protein stimulating properties as suggested by Professor B. M. Hendricks. That these amino acids are utilizable by the

heart for the production of energy seems possible from our results.<sup>6</sup> However, we could not demonstrate any definite building up of creatine. Fisher and Wilhelmi,<sup>36</sup> Davenport, Fisher and Wilhelmi<sup>37</sup> have recently challenged this conclusion.

Experimental myocardial destruction was produced in a large series of rabbits by injection intravenously of caffeine sodium benzoate and adrenalin and similar striking losses of total creatinine were demonstrated in the damaged heart muscle.<sup>38</sup>

In another series of rabbits that we studied with E. H. Schwab<sup>39</sup> we produced aortic insufficiency and the resulting hypertrophied hearts were carefully weighed and analyzed. Half of these animals were digitalized and the other half were not. A series of normal animals and a series of uninjured digitalized animals were simultaneously sacrificed and the heart muscle analyzed. The hypertrophy in the very earliest cases was found to be associated with a relative increase as well as an absolute increase in total creatinine. When hypertrophy became definite and conspicuous as revealed by such gross tests as the heart weight/body weight (H.W./B.W.) ratio, the total creatinine percentage was about normal. In some there was a relative percentage drop in total creatinine; however, the total quantity of creatinine, taking into account the greatly increased weight of the heart, was uniformly definitely elevated. Digitalization usually prevented the percentage drop and thus contributed to distinctly higher total creatinine values. Digitalization showed similar effects upon normal and uninjured hearts in that there was a definite retention or augmentation of the normal total creatinine values.

### HUMAN HEART TOTAL CREATININE STUDIES

In view of the probable significance of the physiological and pathological chemical changes in heart failure, we considered it worth while to continue the clinical as well as the experimental investigation of this interesting albeit difficult subject. We undertook to determine the chemical end results as they appeared in hearts from human autopsy material as well as in the animal hearts. The studies of total creatinine previously reported in groups<sup>40, 41</sup> have been confirmed by the addition of a great many more specimens and analyses.

In our series of over 500 adult human hearts \* to date there have been 374 hearts from patients who died without showing definite evidence of congestive heart failure and 127 from patients who died in congestive heart failure. The hearts from the 374 patients who had not presented evidence of myocardial insufficiency showed average total creatinine levels of 175.3 ( $\pm$ ) 12.5 mg. per cent (standard deviation). In contrast the 127 hearts

\* We are indebted to Prof. Paul Brindley of the Department of Pathology and his staff, particularly Dr. Tom Oliver, Dr. Sion Holley, Dr. M. P. Kelsey, Dr. Jarrett E. Williams, Dr. John S. Shaver, Dr. James Chambers and Gene Thieme. The chemical analyses were made by Peter Erhard.

that had failed contained an average of 125.5 ( $\pm$ ) 25.4 mg. per cent (standard deviation) of total creatinine.

Statistical studies of these data, considering the variations that are presented in this series by applying the "t" test of Fisher, proved the differences to be significant with a P value of less than .01, so that the probability of obtaining such differences by pure chance is practically nil. The low total creatinine values are, therefore, very significant findings in the hearts of patients dead of congestive failure in spite of occasional inex-

TABLE I  
Total Creatinine Content of Hearts from Patients Dead of Various Conditions

Cause of Death	No.	Solids %	Wet Creatine	Dry Creatine	Potassium
Surgery, trauma, tumors.	66	20.42 $\pm$ 0.12 S.D. 1.42	176.7 $\pm$ 1.52 S.D. 18.2	871 $\pm$ 13.6 S.D. 164.2	255.5 $\pm$ 4.7 S.D. 43.7
Hypertension, cerebral hemorrhage.	33	20.72 $\pm$ 0.16 S.D. 1.4	196.0 $\pm$ 3.8 S.D. 32.7	950 $\pm$ 17.1 S.D. 146.7	277 $\pm$ 6.3 S.D. 47.0
Congenital cardiovascular disease. Associated rheumatic, without congestive failure.	15	20.74 $\pm$ 0.26 S.D. 1.5	161.0 $\pm$ 7.8 S.D. 45	771 $\pm$ 31.7 S.D. 182.6	268.1 S.D.
Syphilitic cardiovascular disease without congestive failure.	25	20.85 $\pm$ 0.21 S.D. 1.54	160.0 $\pm$ 1.6 S.D. 37.1	766 $\pm$ 19.6 S.D. 146	247 $\pm$ 9.0 S.D. 53.7
Infectious disease; broncho-pneumonia. Pericarditis, endocarditis.	120	20.63 $\pm$ 0.08 S.D. 1.25	182.0 $\pm$ 2.1 S.D. 33.7	888 $\pm$ 9.8 S.D. 160.8	255. $\pm$ 3.5 S.D. 45.1
Lobar pneumonia.	24	20.24 $\pm$ 0.23 S.D. 1.70	150.0 $\pm$ 5.7 S.D. 36	777 $\pm$ 26.2 S.D. 191	251 $\pm$ 9.5 S.D. 60
Tuberculosis.	27	19.50 $\pm$ 0.17 S.D. 1.30	163.0 $\pm$ 4.1 S.D. 31.7	822 $\pm$ 18.8 S.D. 145	248 $\pm$ 7.6 S.D. 48.9
Uremia.	20	21.18 $\pm$ 0.21 S.D. 1.4	171.5 $\pm$ 4.2 S.D. 28	809.6 $\pm$ 17.6 S.D. 117	252.6 $\pm$ 12.7 S.D. 59.6
Chronic glomerulo-nephritis.	6	20.42	161	791	
Hepatic cirrhosis.	8	20.58	178	919	256
Acute myocardial degeneration.	35	20.09 $\pm$ 0.14 S.D. 1.26	155.5 $\pm$ 3.1 *S.D. 27.8	767 $\pm$ 15.6 *S.D. 139.6	240 $\pm$ 6.9 S.D. 53.1
Anemia; massive hemorrhage.	79	20.18 $\pm$ 0.11 S.D. 1.46	153 $\pm$ 2.4 *S.D. 32.	769.7 $\pm$ 12.5 *S.D. 164.2	236.3 $\pm$ 4.8 S.D. 50.2
Asphyxia.	22	20.00 $\pm$ .20 S.D. 1.42	134.9 $\pm$ 2.9 *S.D. 21.2	674.7 $\pm$ 16.5 *S.D. 114.8	228 $\pm$ 9.6 S.D. 55
Coronary obstruction.	33	20.27 $\pm$ .12 S.D. 1.05	125 $\pm$ 3.0 *S.D. 25.5	605 $\pm$ 17. *S.D. 145.6	240 $\pm$ 2.8 S.D. 44
Congestive failure.	127	20.04 $\pm$ .01 S.D. 1.3	122.5 $\pm$ 1.5 *S.D. 25.4	611 $\pm$ 8.1 *S.D. 135.3	240 $\pm$ 2.8 S.D. 40

\* Statistically significant variation from normal.



TABLE II  
Creatine Content of Hearts from Patients Dead of Coronary Obstruction

Averages 33 Cases Left Ventricle Tot.	Solids 20.27%	Wet Creatine 125.0	Dry Creatine 605	Potassium 240
Infarcted areas	20.20%	85.0	420	217
Uninfarcted areas		145.0	730	
Infarcted areas	17.25%	79.0	387	175
Uninfarcted areas	19.15%	151.0	735	
Infarcted areas	18.80%	78.0	414	264
Uninfarcted areas		152.0	812	
Infarcted areas	20.05%	76.0	380	230
Uninfarcted areas		132.0	657	
Infarcted areas	20.90%	74.0	354	268
Uninfarcted areas		138.0	660	
Infarcted areas	18.05%	61.4	340	147
Uninfarcted areas	21.95%	105.0	480	
Infarcted areas	18.20%	58.5	321	165
Uninfarcted areas	19.70%	110.5	560	
Infarcted areas	18.20%	52.0	318	
Uninfarcted areas	19.70%	100.0	558	
Infarcted areas	19.44%	58.0	277	
Uninfarcted areas	20.94%	78.0	402	
Infarcted areas	20.45%	42.0	205	246.5
Uninfarcted areas	22.75%	122.0	538	
Infarcted areas	17.25%	31.0	180	
Uninfarcted areas	19.15%	151.0	788	

plicable high and low levels. Possible effects of other conditions, particularly those that interfere with oxygenation of the heart, on the creatine levels may be noted in a careful perusal of tables 1 and 2.

Along with our experimental and clinical studies, we have reported corroborative studies of the total creatinine content of hearts from patients

TABLE III  
Phosphorus Values in Human Heart Muscle

Cause of Death	Number of cases	mg. % P. tot.	mg. % Pas.	mg. % Plip.	mg. % Po.
Other than congestive failure	384	189 -3.92	90.1 -2.2	90.9 -4.08	43.9
Congestive failure	127	162 -6.8	72.4 -1.3	89.5 -1.39	41.8

P. tot. = total phosphorus; Pas. = acid soluble phosphorus; Plip = lipid residual phosphorus; Po. = inorganic or other phosphorus.

who had died of coronary thrombosis and cardiac infarction<sup>10</sup> as shown in table 2. Upon analysis the total creatinine content of the infarcted areas of human hearts was far below the concentration of the total creatinine in the uninfarcted myocardium, though this latter was also definitely reduced from normal.

### HUMAN HEART PHOSPHORUS STUDIES

Inasmuch as the total phosphorus and the acid soluble phosphorus may be determined with a fair degree of accuracy and the difference between the two represents very closely the figures obtained directly for the lipid phosphorus, we have extended our chemical analytical procedures to include total phosphorus, acid-soluble phosphorus, lipid phosphorus, ortho or inorganic phosphorus, and potassium. These fractions with the exception of the labile components of the acid-soluble portion, are considered to be stable and not subject to change for 24 to 48 hours after death. The Pas according to Embden contains the individual "activity substances" in the heart muscle.

The inorganic or orthophosphorus values shown in table 3 in heart muscle of patients dead of heart failure and of other conditions did not differ significantly. We found as Wilkins and Cullen<sup>27</sup> had that the total phosphorus values were lowered statistically significantly in the hearts of patients dead of congestive failure.

In our earlier group of cases, the lipid phosphorus, which we determined by difference, seemed significantly lowered in hearts that had failed. Recent adoption of improved analytical procedures, which obviate any absorption by the abrasive of the acid-soluble phosphorus compounds, reveals<sup>42</sup> that the decrease in total phosphorus in the myocardium that has functionally failed is due to a loss of the acid-soluble components: the drop in the average value for the lipid phosphorus is too small to be of statistical significance.

We are unable to attribute any significance, when statistical criteria are applied, to the variations from normal of average values for the potassium content in the different groups.

### COMMENTS

The tabulation of data of hearts from patients who had died without clinical evidences of congestive failure according to the presence of other striking pathological processes was worth while. It is apparent that other conditions which we recognized clinically as possibly contributory to heart failure may play a rôle in changing the creatine and phosphorus content of the heart muscle. In hearts from patients who presented striking anemia, conspicuous asphyxia as a result of strangling, acute or chronic pulmonary disease, syphilitic aortitis, or coronary artery disease, there were definite subnormal myocardial total creatinine values. The hearts of those with infectious diseases, rheumatic valvular disease, and hypertension with cere-

bral hemorrhage showed fairly normal to elevated creatine values. The lowered total creatinine in pneumonia heart is interesting and may be proved to be significant. The apparent tendency of digitalis to cause an elevation of total creatinine is significant of a chemical myocardial action.

The total phosphorus and acid soluble phosphorus fractions were decreased in hearts that had failed; the small number of cases in the other groups make the variations of doubtful significance.

In the light of these chemical findings, it seems suggestive at least that total creatinine and creatine, total phosphorus and acid soluble phosphorus losses usually accompany heart failure. Whether the chemical changes are the cause of the heart failure or the result of the heart failure is a question that should be raised and as yet cannot be answered. Further experimental evidence is needed. We must substantiate our contention that the losses of total creatinine and phosphates are the factors that lead to myocardial weakness.

It has been generally accepted that in anoxemia, in asphyxia and in aglycemia there is a failure of resynthesis of creatine phosphate. These same conditions, we concluded, might lead to creatine and phosphorus losses from human hearts and ultimate cardiac weakness.<sup>40, 41</sup> Consideration of such facts and our findings lead us to extend Harrison's<sup>4</sup> physical theory of the anoxemic etiology of circulatory failure to include inevitable biochemical changes in heart muscle to account for myocardial insufficiency.

### CONCLUSION

The chemical theory of the mechanism of heart failure has much evidence in its favor.

Even though the theory seems substantiated and the indications simple yet there is, thus far, little that may be done about it.

The perfusion and feeding experiments with the precursors of creatine phosphoric acid have not yet been successful in causing it to build up.

The correction of chronic conditions that lead to anoxemia are in order so far as it is possible to prevent the further dissipation of the essential activity substances.

Oxygen therapy is in order but still is rather impractical. It is so often impossible to get the  $O_2$  to the cells where it is needed.

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# MACROCYTIC ANEMIA, OTHER THAN PERNICIOUS ANEMIA, ASSOCIATED WITH LESIONS OF THE GASTROINTESTINAL TRACT\*

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A macrocytic anemia may be defined as an anemia in which there is an increase in the number of red blood cells of the circulating blood having a diameter greater than 7.5 microns, and a mean corpuscular volume which exceeds 96 cubic microns. In such an anemia the color index usually is one or higher. It is generally considered to be due to defective blood formation and is frequently controlled by anti-pernicious anemia medication but is not ordinarily benefited by iron therapy.

An anemia of this type is characteristically found in true Addisonian pernicious anemia, in the so-called "tropical anemia" and some cases of sprue, in myxedema, occasionally in leukemia, and for a short interval immediately following an acute hemorrhage. Finally, such an anemia may be the result of a dietary deficiency or various gastrointestinal disturbances.

It is with these latter two causes that this study is primarily concerned. It is not the purpose of this paper to attempt to give an extensive review of the literature concerning the relation of the gastrointestinal tract to the macrocytic anemias. During the past decade, largely through the work of Castle and his coworkers,<sup>1, 2, 3, 4</sup> Meulengracht,<sup>5-9</sup> Goldhamer<sup>10-14</sup> and others,<sup>15-20, 22</sup> our knowledge concerning the relation of the gastrointestinal tract to pernicious anemia and other macrocytic anemias has been classified and the apparent diverse causes for such an anemia have been correlated and an understanding concerning their inter-relationship has now been reached.

In order to understand these, it is necessary to review briefly the normal process by which the red blood cells are developed and released to the peripheral blood. This is accomplished, according to Castle,<sup>1, 2, 3, 4</sup> as follows: Some unidentified substance which is called the "extrinsic factor" is ingested in the diet and this reacts with an "intrinsic factor," probably an enzyme, which is contained in the gastric secretions. As a result of this reaction, a substance is formed which controls the rate of formation of red blood cells in the bone marrow. Since the red blood cells are not normally released until they are mature, any disturbance in the formation of the substance controlling the maturation of the erythrocytes, will diminish the number which are released to the peripheral blood and an anemia will develop. It has been demonstrated by Castle that pernicious anemia is due to

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From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan.

a gastric defect which results in absence of, or, as Goldhamer<sup>10,11</sup> has shown, a diminution of the intrinsic factor, while the macrocytic anemia which may be present in sprue is thought to be due in some cases to a lack of the extrinsic factor.<sup>21</sup> Even though the intrinsic and extrinsic factor reaction occurs in an individual, other conditions may prevail which prevent the erythrocyte maturing substance from performing its normal function. For example, there may be a failure to absorb the material which results from the interaction between the extrinsic and intrinsic factors, as a result of intestinal anastomoses or stricture.<sup>5</sup> Furthermore, it is now generally accepted that extensive liver disease<sup>13, 14, 20</sup> which prevents the storage of the erythrocyte maturing substance, may cause a macrocytic anemia.

The gastrointestinal lesions which may be associated with a macrocytic anemia may be stated briefly as follows: Total gastrectomy, extensive infiltrative carcinoma of the stomach, various lesions of the intestines such as stricture and anastomoses, and extensive liver disease which may be the result of widespread cirrhosis or some other process such as an acute hepatitis.

These blood changes are important for several reasons. From a practical standpoint macrocytic anemias are of significance because of the therapeutic indications. They yield, in many instances, to anti-pernicious anemia medication, especially to the parenteral administration of liver extract. On the other hand, iron, while it may be of value in rare instances, ordinarily is of no benefit. From a theoretical point of view, the various gastrointestinal lesions which cause such an anemia are of the greatest interest, not only from the standpoint of etiology but also because they make clear the mechanism by which the formation of red blood cells is normally controlled.

For the past 11 years it has been our privilege to observe a large group of patients with pernicious anemia at the Simpson Memorial Institute. During the course of our studies a number of patients with macrocytic anemia have been observed who have illustrated very strikingly the various types of gastrointestinal lesions which may cause such an alteration in the blood.

The following are the case histories of the patients on whom these observations were made.

#### CASE REPORTS

*Case 1.* V. M., female, aged 27, was admitted May 21, 1929 with chief complaints of vomiting, weakness and cramp-like pain in the stomach. She reported that for about a year she had had "gastric upsets" characterized by nausea, vomiting and severe cramp-like abdominal pain. These symptoms gradually increased in intensity and for a few weeks before admission she had been unable to retain even fluids. There had been a 20 pound weight loss during the present illness. A few weeks before admission she had been troubled with dyspnea, palpitation, dizziness and headache.

Physical examination showed an emaciated, under-nourished female with mild pallor. There was a soft tender mass above and to the left of the umbilicus. The

red blood cell count was 4.27 million per cu. mm., hemoglobin 70 per cent. Gastric analysis after injection of histamine showed no free hydrochloric acid. The Kahn reaction was four plus. Roentgen-ray examination showed an irregularity at the prepyloric region of the stomach and on the greater curvature, with complete obstruction. The most probable diagnosis was hereditary lues and the patient was treated with antiluetic therapy for a short interval. On account of the vomiting and inability to retain fluids, however, it was thought an operation should be performed without further delay and the lower half of the stomach was resected and a gastrojejunostomy was done. About three years later she again had complaints of eructation of gas, nausea and vomiting. Her appetite had been poor and there had been a 12 pound weight loss. Physical examination showed an emaciated female with very marked pallor. The sclerae were icteric. The red blood cell count was 1.18 million per cu. mm., hemoglobin 23 per cent. Gastric analysis following injection of histamine showed no free hydrochloric acid. The patient was treated with oral and parenteral liver extract which caused a characteristic reticulocyte response with a rapid increase of the red blood cells and hemoglobin to normal. The patient has not been seen since leaving the hospital but a letter from her in October 1935 states that she felt perfectly well. After her discharge from the hospital she had eaten some liver every week but had had no other form of therapy. The reaction of the blood to treatment is shown in chart 1.

V.M., NO. 215916.

## GASTRECTOMY (GUMMA OF STOMACH).

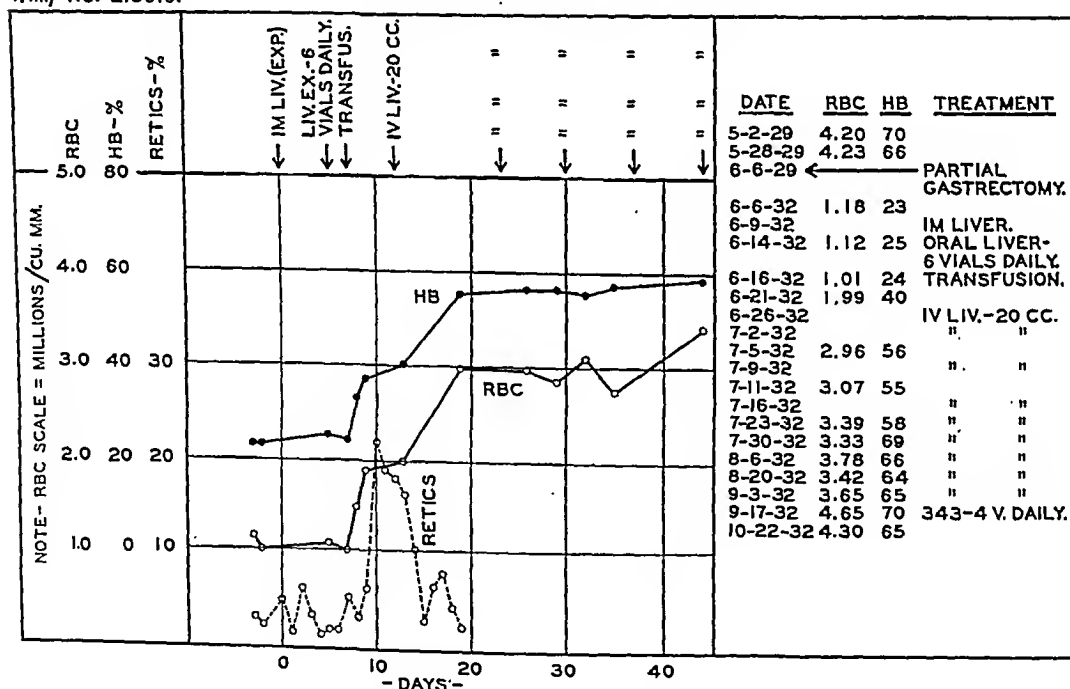


CHART 1. The effect of oral and parenteral liver therapy on the anemia resulting from gastrectomy.

Case 2. A. F., a male, 38 years of age, was admitted to the hospital November 24, 1933, with the chief complaint of pain over the heart.

Present Illness: For four or five months the patient had suffered from vague precordial and epigastric pain which was dull and aching in character. This was brought on by eating, and usually persisted throughout the day. There had been some distress and belching of gas, and also a decrease of 12 pounds in body weight during the present illness.



Physical examination showed nothing of importance except evidence of weight loss. The red blood cell count was not done but the hemoglobin was found to be 92 per cent. Fasting gastric analysis showed no free hydrochloric acid. Roentgen-ray examination disclosed a neoplasm of the posterior wall of the stomach occupying the middle and lower thirds of this organ. Partial gastrectomy and gastrojejunostomy were done on November 7, 1933, at which time approximately two-thirds of the stomach was removed. The pathologic report was medullary carcinoma of the stomach. On April 10, 1936, about three years after the operation, the patient was admitted for a second time complaining of increasing fatigue, weakness, dyspnea and palpitation on exertion. There had been some edema of the lower extremities. Physical examination showed nothing of importance except pallor and pitting edema of the ankles. His red blood cell count was 1.79 million per cu. mm., hemoglobin 40 per cent. The patient was given intramuscular liver extract (Parke, Davis and Co.)

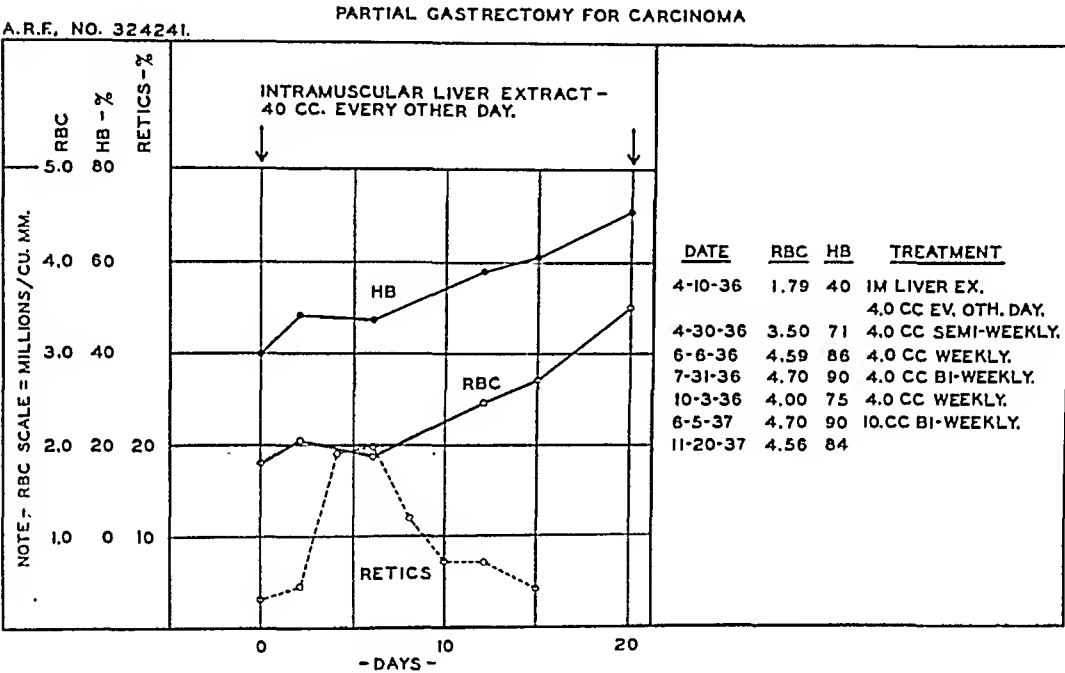


CHART 2. The effect of parenteral liver extract on the macrocytic anemia occurring after gastrectomy.

4 c.c. every other day, which resulted in a reticulocyte rise which reached a peak of 20 per cent. The changes in the blood are shown in chart 2.

Case 3. J. K., a male, 53 years of age, was admitted July 28, 1929 with the chief complaint of a discharging sinus of the chest.

Present Illness: In October 1928 he stated that he developed pleurisy with effusion and purulent fluid was said to have been aspirated on three occasions from the pleural cavity. At this time a microcytic anemia was present which was attributed to infection. He entered the University Hospital and was treated by irrigation and drainage of the empyema cavity. Early in 1930, a thoracoplasty was done, at which time there was a marked increase in the anemia. Following iron medication, however, his blood returned almost to normal. In 1932 he returned to the hospital stating that for four weeks he had suffered with epigastric pain, marked constipation and nausea and vomiting. Roentgen-ray examination showed a polypoid neoplastic mass in the upper two-thirds of the stomach. His red blood cell count was found to be 3.00 million per cu. mm. and hemoglobin 30 per cent.

Gastric resection was performed and approximately two-thirds of the stomach was removed. Prior to the operation the patient had a blood transfusion and was given iron medication for a considerable period of time. For a period of approximately a year, however, he had no anti-anemic therapy and about the middle of 1934 he returned to the hospital, at which time he had a definite macrocytic anemia with a red blood cell count of 2.80 million per cu. mm. and hemoglobin 80 per cent. He was then given intramuscular liver extract and as a result his red blood cell count and hemoglobin became practically normal after three months. He then practically discontinued therapy and when seen early in 1937 he again had a macrocytic anemia with a hemoglobin of 58 per cent and red blood cell count of 2.6 million per cu. mm.

In summary then, the patient first had a microcytic anemia as a result of in-

J.K., NO. 220714.

#### GASTRECTOMY FOR CARCINOMA

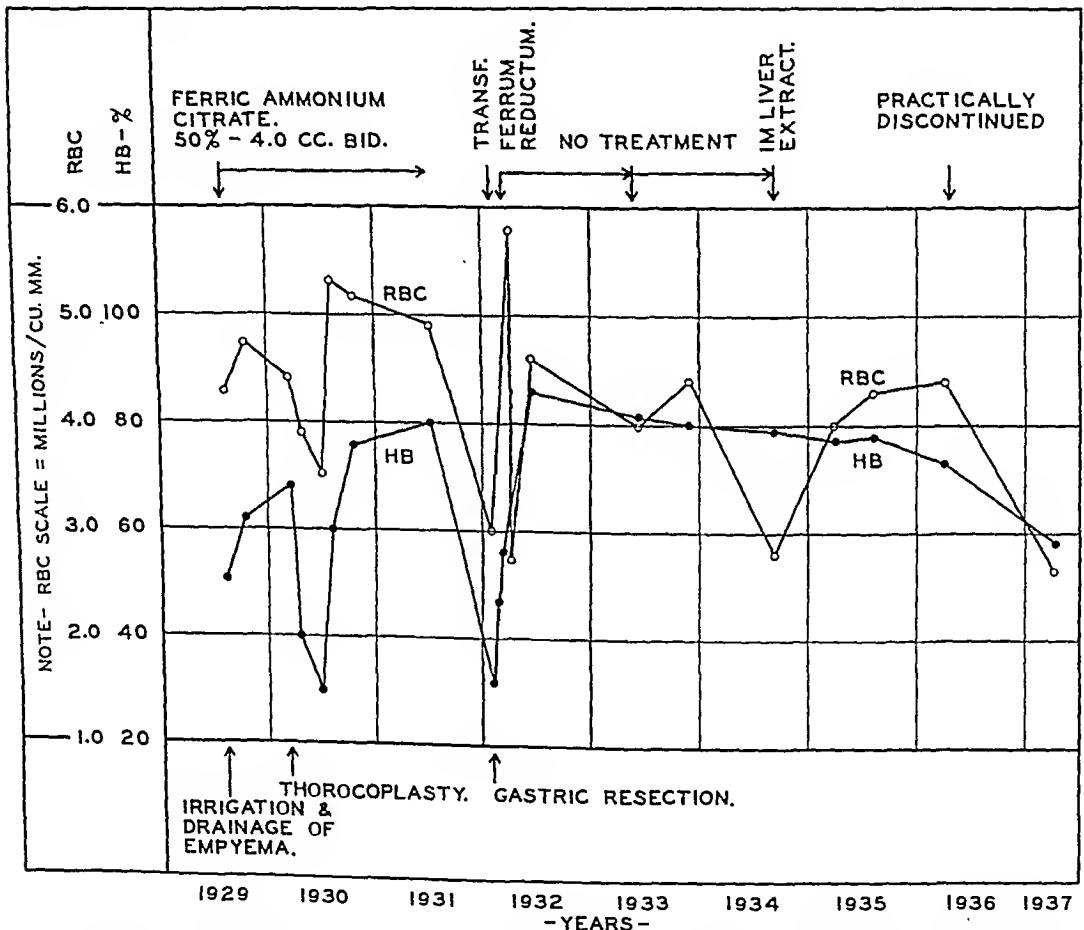


CHART 3. The occurrence of a microcytic anemia associated with infection and carcinoma of the stomach and the subsequent development of a macrocytic anemia, following gastrectomy, which was controlled with intramuscular liver extract.

fection, which disappeared when this was controlled, and following the administration of iron. Some time later he again developed a microcytic anemia which was associated with a neoplasm of the stomach. Following gastric resection, he was found to have a macrocytic type of anemia which was controlled by liver extract for a time, but recurred when the liver extract medication was stopped by the patient. The changes in the blood are shown in chart 3.

Case 4. J. G. K., a male, 63 years of age, was admitted January 30, 1934, with the chief complaints of fatigability, weakness, dyspnea and palpitation.

Present Illness: The onset was four months previously when the patient noted greatly increased weakness and ease of fatigue. This progressed and two months prior to admission he developed dyspnea and palpitation on exertion. Pallor was noted and icterus had been present for three weeks. There had been some distress following meals for a month and a five pound weight loss.

The family history is of interest because his father died of pernicious anemia and the mother and one sister had cancer.

Physical examination showed an elderly male who appeared to be critically ill. The skin was pale and icteric. There was some atrophy of the tip of the tongue and along the margins but it was not the characteristic tongue seen in pernicious anemia. Neurological examination was negative. Gastric analysis showed no free hydrochloric acid. The icterus index was 40, the blood bilirubin was 1.6 mg. per 100 c.c., the red blood cells 1.30 million per cu. mm., hemoglobin 32 per cent (Sahli).

This patient's gastric juice was obtained and after incubation with hamburger steak, according to the technic of Castle, it was administered to another patient with pernicious anemia in relapse, and no reticulocyte response was observed, which indicated an absence of the intrinsic factor.

J.K., NO. 329416.

## CARCINOMA OF STOMACH

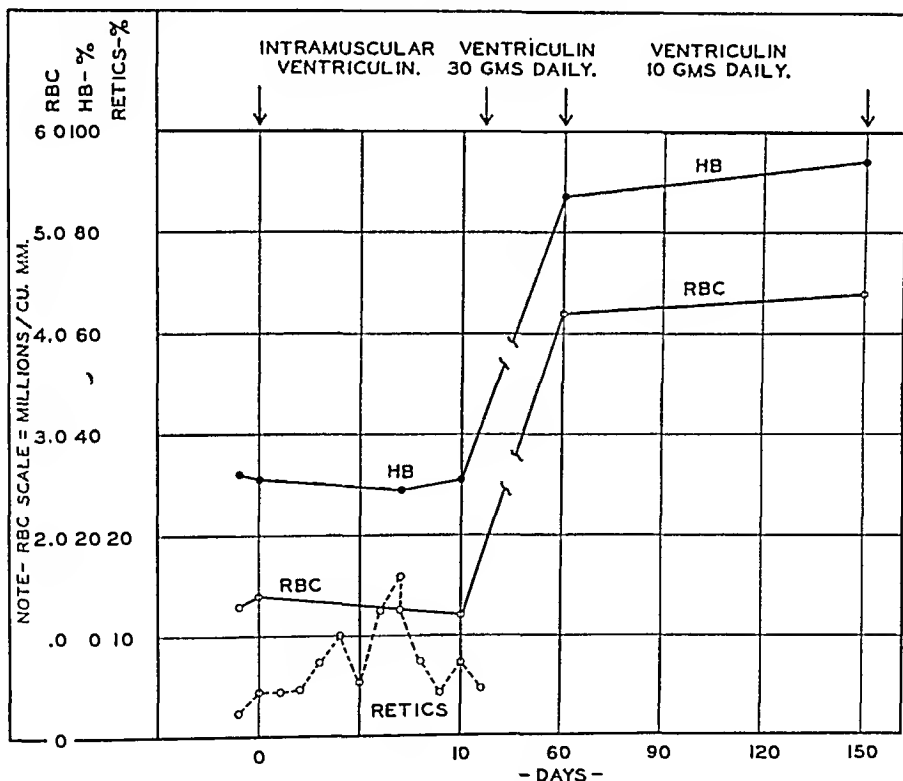


CHART 4. The effect of desiccated stomach on the macrocytic anemia due to *linitis plastica*.

The patient was given an intramuscular injection of an experimental preparation of Ventriculin which possibly was of weak potency. This was followed by a reticulocyte response of 16 per cent on the seventh day of treatment. The patient was discharged from the hospital with instructions to take 30 grams of Ventriculin daily. He returned on April 30, 1934, three months after leaving the hospital, at which time his red blood cell count was found to be 4.22 million per cu. mm., hemoglobin 87 per cent. He returned again on July 31, 1934, stating that for the past month he had had

distress after meals and some nausea and vomiting. His red blood cell count was then 4.38 million per cu. mm., hemoglobin 94 per cent. There had been a 25 pound weight loss during the preceding two months. Roentgen-ray examination at this time showed evidence of *linitis plastica*. Although it cannot be proved, it is assumed that the patient had *linitis plastica* on the first admission and this extensive infiltrating malignant growth had destroyed the gastric glands and as a result there was a lack of the intrinsic factor in the gastric juice. The changes in the blood are shown in chart 4.

Case 5. M. R. N., a female, 46 years of age, was admitted to the hospital on August 10, 1932, with the chief complaints of "weakness and lack of endurance." In 1927 she had three abdominal operations, the first for adhesions causing acute obstruction; at the second, a few months later, four feet of intestines were removed and an anastomosis was done; and at the third operation an anastomosis of the ileum

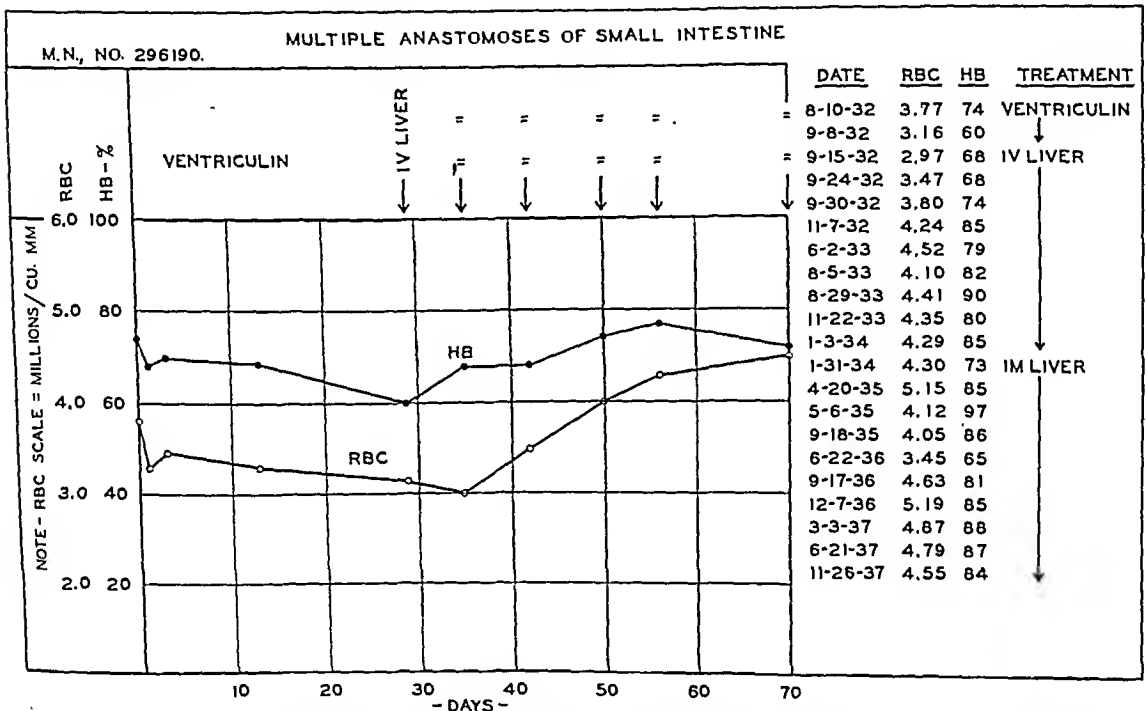


CHART 5. The failure of response to desiccated hog stomach and subsequent elimination by parenteral therapy of the macrocytic anemia associated with multiple anastomoses of the small intestines.

to the ascending colon was performed. The patient remained in good health except for attacks of diarrhea until six or eight months previous to admission, at which time she had influenza which was followed by a prolonged convalescence. At this time she was told her red blood cell count was 2.00 million per cu. mm. She suffered from considerable gaseous distention and had frequent attacks of diarrhea. Occasionally she had rather severe cramp-like abdominal pain. There had been a loss of eight to ten pounds in body weight in the past six months.

Physical Examination: Negative except for evidence of weight loss and a barely palpable liver and spleen. Her red blood cell count was 3.30 million per cu. mm., hemoglobin 70 per cent. Gastric analysis following injection of histamine showed the presence of free hydrochloric acid. The patient was given Ventriculin, 40 grams daily, orally, but the red blood cell count and hemoglobin diminished slightly over a period of 30 days. She then received intravenous liver extract which resulted in a

prompt rise in the red blood cells and hemoglobin to normal. After receiving this form of therapy for approximately two years she was given intramuscular liver extract which maintained her blood at a normal level except for intervals when she grew lax in her treatment. When last seen on November 26, 1937, her red blood cell count was 4.55 million per cu. mm. and hemoglobin 84 per cent. Changes in the blood following treatment are shown in chart 5.

Case 6. C. H., a male, 31 years of age, was admitted on September 27, 1935, with the chief complaint of "abdominal pain." He stated that he had suffered from constant generalized abdominal pain for 12 years, which was not related to meals. Other complaints were belching, flatulence, and intermittent diarrhea and constipation. There had been some nausea and vomiting. No change had been noted in the appearance of the stools. He had noticed a transient swelling in the right lower quadrant accompanied by a gurgling sensation in this area at intervals. There had been a marked weight loss. The patient had an appendectomy in 1923 and in June 1935 an abdominal operation for relief of adhesions.

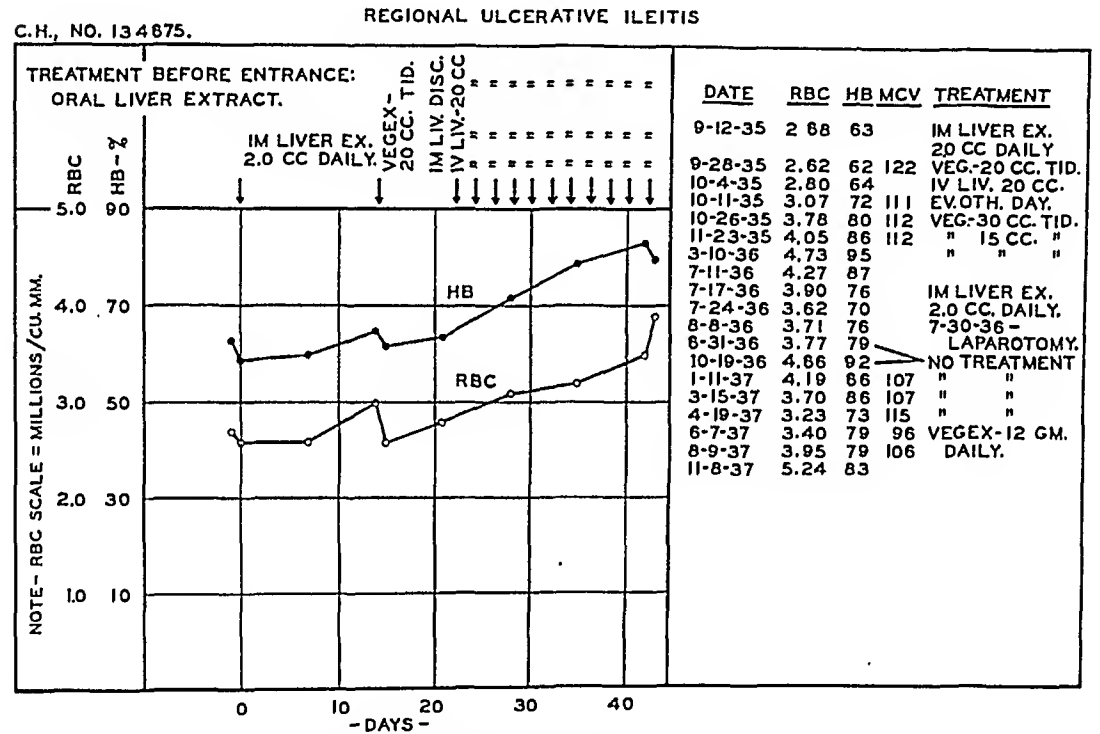


CHART 6. The effect of oral and parenteral therapy on the macrocytic anemia due to intestinal obstruction and spontaneous remission following removal of the intestinal lesion.

Physical Examination: The patient was a poorly nourished, emaciated male, showing some pallor. The tongue was smooth, and showed definite atrophy of the papillae which resembled the change observed in patients with pernicious anemia. There was tympany and distention of the abdomen, and tenderness in the right lower quadrant. The neurological examination was negative. On his first admission the red blood cell count was 2.19 million per cu. mm., hemoglobin 65 per cent. Fifty-eight per cent of the cells were larger than 7.5 microns and the mean corpuscular volume was 122 cu. microns. Gastric analysis following administration of histamine showed the presence of free hydrochloric acid. Roentgen-ray examination indicated that there was a delayed emptying of the small intestine. He was treated with intramuscular liver extract (Parke, Davis & Co.) 2 c.c. daily and following this

there was a reticulocyte rise to a peak of 5.8 per cent. In addition he was given Vegex, 20 c.c. three times daily. Later 20 c.c. of liver extract (amount derived from 100 grams of liver) were given daily for 11 days. With this his red blood cell count rose promptly to 3.90 million per cu. mm. and hemoglobin to 80 per cent. The patient was then treated with variable amounts of Vegex. The patient was re-admitted on July 13, 1936, with a recurrence of all abdominal symptoms. On this admission the red blood cell count was 4.20 million per cu. mm. and hemoglobin 87 per cent. On July 30, 1936 a laparotomy was performed and 2½ feet of lower ileum were resected. The pathological report was regional ileitis. The patient was discharged without further treatment. On October 19, 1936, the red blood cell count was 4.60 million per cu. mm., hemoglobin 92 per cent. He had a recurrence of his symptoms and returned on April 19, 1937 with a red blood cell count of 3.25 million per cu. mm., hemoglobin 73 per cent. The mean corpuscular volume was then 115 cu. microns. He was again treated with Vegex and when last seen on November 8, 1937, the red blood cell count was 5.24 million per cu. mm., hemoglobin 83 per cent. He still complained of abdominal cramps. The changes in the blood are shown in chart 6.

Case 7. M. P., a female 52 years of age, was admitted December 10, 1936, with chief complaint of "diarrhea."

Present Illness: Patient stated that during the past year she had had 10 to 12 watery stools daily. She had not noticed that they contained blood or mucus. Occasionally she had had nausea and vomiting, and there had been a weight loss of 40 pounds in the last ten months. She had had frequent attacks of glossitis. During this time the patient had been on an adequate diet.

M.P., NO. 192923.

#### ILEO-COLIC FISTULA

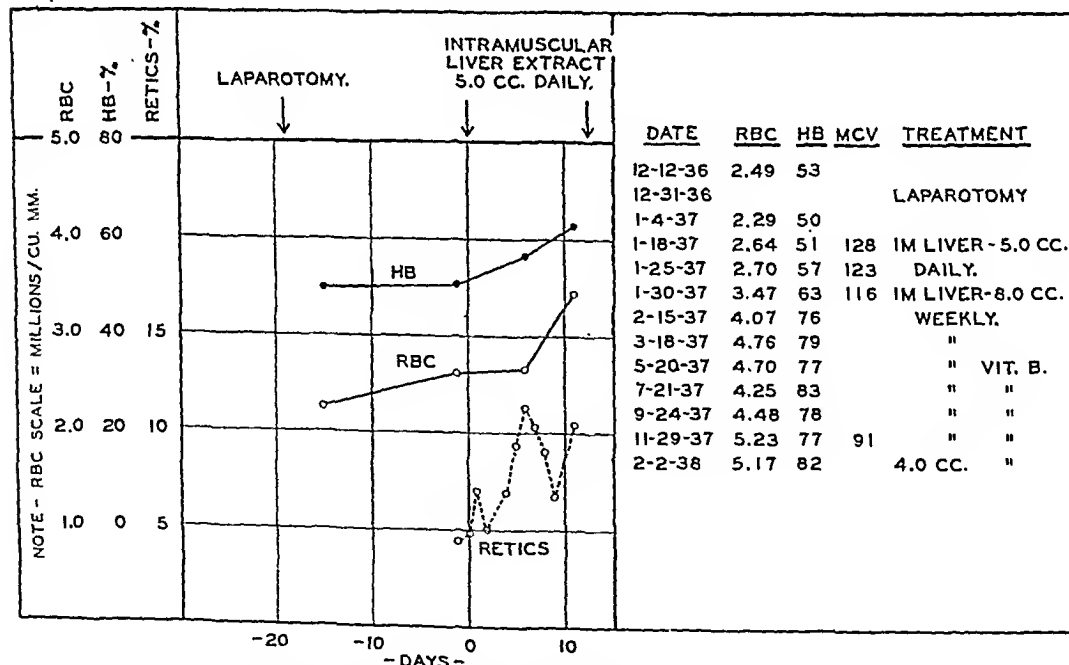


CHART 7. The hematologic response to effective parenteral therapy in a patient with an ileocolic fistula.

Physical examination showed an emaciated, pale female. The tongue was clean and appeared to be normal. The abdominal examination was negative. There was slight edema of the ankles. The red blood cell count was 2.49 million per cu. mm. and the hemoglobin was 53 per cent. Fifty-three per cent of the cells were larger

than normal. The gastric analysis showed free hydrochloric acid. Roentgen-ray examination of the gastrointestinal tract disclosed an ileocecal fistula. The patient was operated upon December 31, 1936 and an unsuccessful attempt was made to repair this condition. It was thought that the patient had had an old tuberculous salpingitis with a localized peritonitis which accounted for the condition, but biopsy showed nothing but chronic infection. The patient was placed on intramuscular liver extract, 5 c.c. daily, which was followed by a reticulocyte rise to 12 per cent. After the red blood cell count reached approximately 4.00 million per cu. mm., the patient was given weekly injections of liver extract intramuscularly, 8 c.c. (Parke, Davis & Co.) and in addition she received vitamin B orally. Her red blood cell count when last seen on February 2, 1938, was normal, as well as her hemoglobin, and there had been a gain in weight of 29 pounds since the patient was first seen. The response of her blood to treatment is shown in chart 7.

*Case 8.* W. T. M., a male, 40 years of age, was admitted November 16, 1931 with the chief complaint of "abdominal pain."

**Present Illness:** In January 1930 the patient first noted abdominal cramps and sharp shooting pain below the right rib margin. This pain came in attacks and persisted for about two hours. Once it was accompanied by vomiting, diarrhea and jaundice which persisted for one week. The patient has had a number of such attacks.

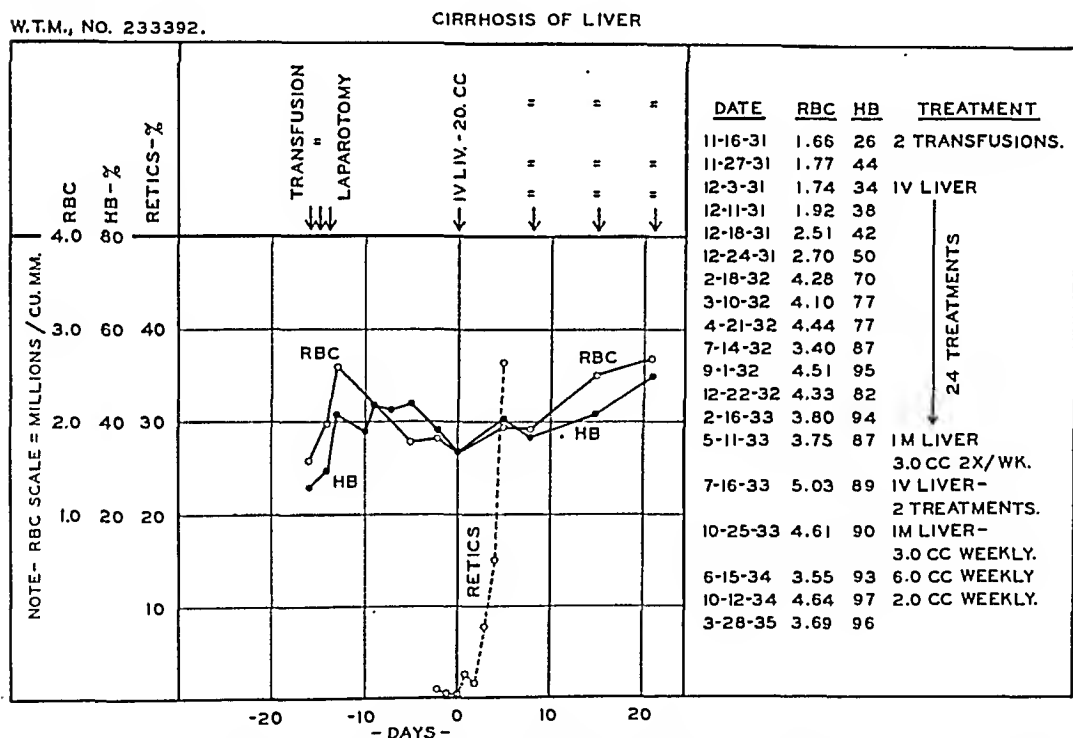


CHART 8. The hematologic response in cirrhosis of the liver following the administration of parenteral liver extract.

**Physical Examination:** There was very definite evidence of weight loss, and the skin was icteric. The liver was moderately enlarged and there was tenderness in the upper quadrants. The spleen was barely palpable. The red blood cell count was 1.66 million per cu. mm., hemoglobin 26 per cent. The roentgen-ray examination was negative. The patient was thought to have some type of abdominal malignant growth and as a result exploratory laparotomy was done on November 19, 1931. No neo-

plasm was noted but the patient was found to have a definite cirrhosis of the liver. Two blood transfusions were given and later intravenous liver extract was administered. As a result, there was a prompt increase in the reticulocytes which reached a peak of 36 per cent, at which time the patient left the hospital. Subsequently, with additional intravenous treatments of liver extract and later with intramuscular treatments, the blood returned to normal. The blood was not maintained continuously at a normal level because the patient received some experimental liver extract which possibly was not of full potency, and later he administered the treatments himself and became lax in following directions. The response of his blood to treatment is shown in chart 8.

*Case 9.* R. M., a male, 55 years of age, was admitted October 29, 1931, with the chief complaint of "pain in the abdomen."

**Present Illness:** The patient complained that he had suffered from abdominal discomfort below the umbilicus for three months prior to admission. It was generalized and gradually became more severe. Also he had been troubled with nausea but there had been no vomiting. A short time before admission he had developed moderate dyspnea and palpitation on exertion. There had been a 10 pound weight loss.

Physical examination showed evidence of weight loss. The abdomen was mod-

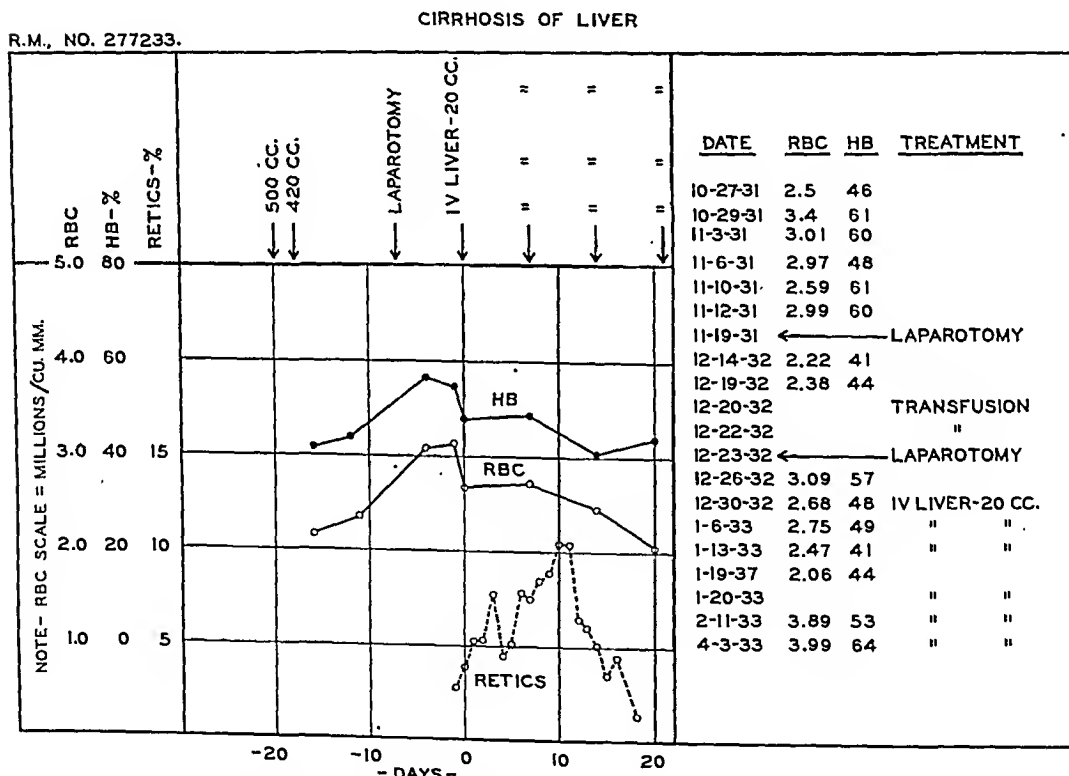


CHART 9. The effect of intravenous liver extract on hematopoiesis in a patient with hepatic cirrhosis.

erately distended and there was generalized tenderness. Slight pitting edema was present. The red blood cell count was 2.51 million per cu. mm., hemoglobin 46 per cent. Gastric analysis showed free hydrochloric acid present. The patient was thought to have an abdominal malignant growth and this diagnosis led to a laparotomy on November 19, 1931. No neoplasm was found but the patient was observed to have cirrhosis of the liver. About one year later the patient returned stating that he had had a recurrence of all his symptoms which had troubled him for the previous



six months. Physical examination was the same as on previous admission. Roentgen-ray examination at this time showed what was considered to be an obstructive cancer of the transverse colon. The red blood cell count was 2.22 million per cu. mm., hemoglobin 41 per cent. On December 23, 1932 laparotomy was performed and the defect observed in the roentgen-ray was found to be due to marked adhesions at the hepatic flexure. A few days after the operation he was given injections of liver extract intravenously which caused a reticulocyte response and an increase in the red blood cells to approximately 4.00 million, and of the hemoglobin to 64 per cent. He was last seen on March 3, 1933, and his present condition is not known. The changes in the blood following treatment are shown in chart 9.

**Case 10.** R. J., a female, 32 years of age, was admitted to the hospital on March 22, 1937 with the chief complaints of dyspnea, palpitation and weakness. Four and a half months before admission, at which time the patient was seven months pregnant, she had developed dyspnea on exertion, mild generalized abdominal pain and had noted a few purpuric areas around the umbilicus. At this time a marked pallor appeared. The red blood cell count was said to be 2.00 million per cu. mm. at that time. She was treated with "Ventriculin and Iron" and by two transfusions, and improved somewhat. At the eighth month of pregnancy her red blood cell count was reported as being 1.80 million per cu. mm. Labor was induced at this time. Following this the dyspnea, palpitation and weakness increased and she was treated with transfusions, intramuscular liver extract and iron. There was a 10 pound weight loss.

#### ACUTE HEPATITIS ASSOCIATED WITH PREGNANCY

R. J., NO. 399050.

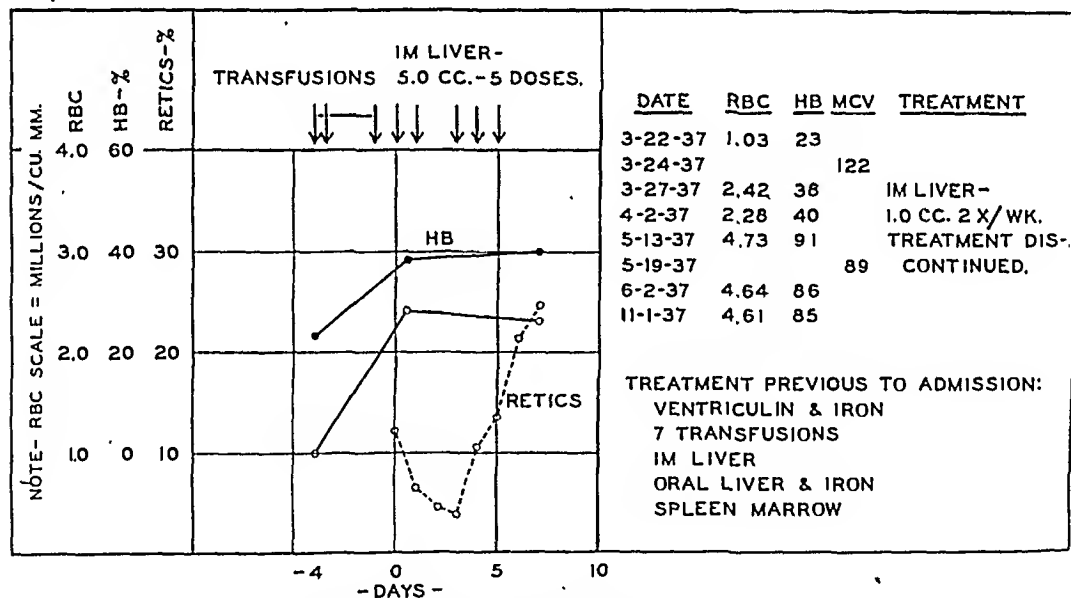


CHART 10. An induced remission due to parenteral liver therapy in the macrocytic anemia associated with acute hepatitis.

Physical examination showed a pale, emaciated female. The liver reached the level of the umbilicus and the spleen descended 4 cm. below the left costal margin. There was pitting edema of the ankles. The red blood cell count was 1.03 million per cu. mm., hemoglobin 23 per cent. Bilirubin 1.5 mg. per 100 c.c. Mean corpuscular volume 122 cu. microns. Gastric analysis following administration of histamine revealed an absence of free hydrochloric acid. Sternal puncture showed increased erythropoiesis. Patient was thought to have an acute hepatitis associated with

pregnancy and the liver disturbance was considered to be the cause of the anemia. She was treated with three blood transfusions and at the same time given intramuscular injections of liver extract (Parke, Davis & Company) 5 c.c. daily for three days. At the end of this time the reticulocytes rose to 21.5 per cent; the patient felt much improved and she left the hospital. Subsequent blood examinations showed the blood had returned to normal. She had been receiving intramuscular liver extract 1 c.c. two times weekly but after the blood was found to be normal, May 13, 1937, her anti-pernicious anemia therapy was discontinued. The changes in the patient's blood are shown in chart 10.

### DISCUSSION

The question might be raised quite properly concerning the causal relationship between the gastric lesion and the macrocytic anemia. It is, of course, possible that, in some instances there might be a coincidental association of the two conditions and no etiological relationship. Studies to determine the presence or absence of the intrinsic factor in the stomach would shed some light on this question but unfortunately it was possible to determine this only in Case 5, in which this factor was found to be absent. Its absence was interpreted as being due to an extensive malignant involvement (linitis plastica) of the entire stomach and a destruction of the gastric secreting glands which produce the intrinsic factor. One reason which indicates that intestinal lesions are responsible for this type of anemia is the disappearance of the anemia when the intestinal lesion is repaired. In Case 7, for example, the red blood cell count returned to normal following resection of the small intestine for partial obstruction, at which time the patient was not receiving any anti-anemic therapy. It is also of significance that the anemia reappeared when the partial obstruction again developed.

Further evidence that the group of patients which was studied did not have a true Addisonian anemia which by chance was associated with some gastrointestinal lesions is that three of the 10 patients considered had free hydrochloric acid present in the gastric secretions (table 1). Also five of the seven patients about whom information was obtained did not have paresthesia of the hands and feet which is present in 90 per cent of patients with pernicious anemia. Furthermore, only one patient had recurrent glossitis, which is present in approximately 65 per cent of patients with Addisonian anemia. In eight patients where data were recorded, a definite statement is made saying that there was no atrophy of the tongue. This sign is present in about half of the patients with pernicious anemia.

The action of autolyzed yeast (Vegex) on the reticulocytes, red blood cells and hemoglobin of a patient with typical pernicious anemia is shown in chart 11. The fact that some patients with pernicious anemia show an improvement following the ingestion of this substance is of more theoretical than practical interest since more satisfactory therapeutic results are obtained by the administration of liver and stomach preparations. The mode of action of yeast in these patients is not clearly understood. Ungley<sup>23, 24, 25</sup> considers that it probably acts by virtue of its content of extrinsic factor and

TABLE I

Pt.	Case No.	Sex	Age	Nature Oper.	Time before Anemia Disc.	RBC Mill.	Hb. %	Achlor-hydrin	Glossitis	Atrophy Tongue	Pares-thesia Hands and Feet	Vibr. Sense	Mot. and Pos.	Resp. to Therapy	Type of Therapy	Diagnosis
VM	1	F.	27	Partial resect. stomach	33 mos.	1.2	23	Yes	No	No	No	N	N	Good	I. V. Oral Liv. Ext.	Gumma stomach
AF	2	M.	38	Partial resect. stomach	29 mos.	1.8	40	Yes	No	No	No	N	N	Good	I. M. Liv. Ext.	Cancer stomach
JK	3	M.	53	Partial gastrec.	30 mos.	2.8	79	—	—	—	—	—	—	Good	I. M. Liv. Ext.	Cancer stomach
JGK	4	M.	63	None	—	1.3	32	Yes	No	No	No	N	N	Good	Ventriculin	Linitis plastica
MRN	5	F.	46	3 short circuit. Op.	5 yrs.	3.3	70	Yes	No	No	—	N	N	Good	I. M. Liv. Ext.	Multiple anastomoses bowel
CH	6	M.	31	Resect. intestine	—	2.7	63	No	No	No	No	N	N	Good	I. M. Liv. Ext. Veget	Reg. ulcer; ileitis
MP	7	F.	52	Lap. <sup>1</sup>	—	2.5	53	No	Yes	No	Yes	Dim.	N	Good	I. M. Liv. Ext.	Ileocolic fistula
WTM	8	M.	40	Exp. lap.	—	1.7	26	Yes	—	No	—	N	N	Good	I. V. I. M. Liv. Ext.	Cirrhosis liver
RM	9	M.	55	Two exp. lap.	—	2.5	46	No	No	No	Yes	N	N	Good	I. V. Liv. Ext.	Cirrhosis liver
RJ	10	F.	32	None	—	1.0	23	Yes	No	—	No	N	N	Good	I. M. Liv. Ext.	Acute hepatitis

<sup>1</sup> An unsuccessful attempt to relieve ileo-colic fistula.

cites observations which he had previously reported showing that it is not effective when administered parenterally. On the other hand, Davidson<sup>26</sup> concludes that autolyzed yeast contains some hemopoietic principle. Russell<sup>27</sup> suggests that small amounts of the intrinsic factor are present in the

E.F., NO. 306787.

## PERNICIOUS ANEMIA

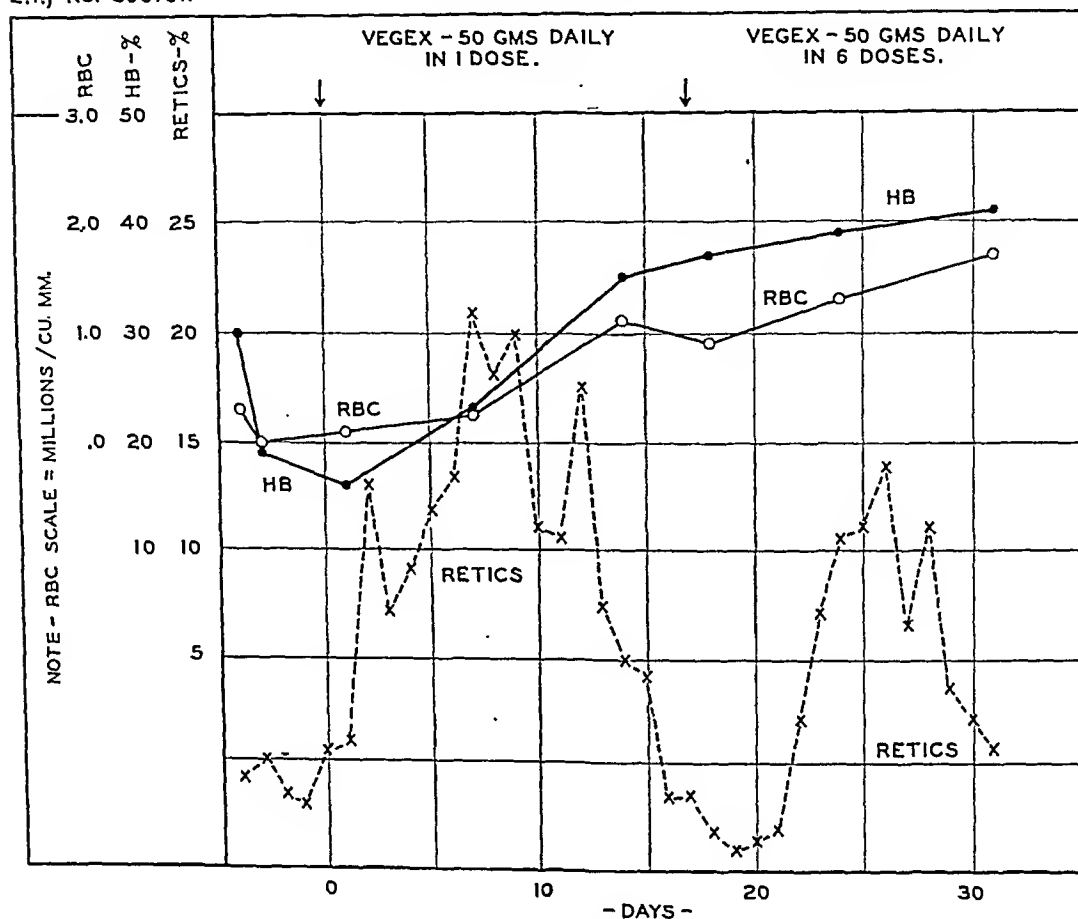


CHART 11. The action of autolyzed yeast (Vegex) on the reticulocytes, red blood cell count and hemoglobin of patients with pernicious anemia.

gastric secretion in some patients with pernicious anemia (and this has been substantiated by Goldhamer<sup>11</sup>), and that some red blood cell maturing substance is produced when large amounts of the extrinsic factor are administered in the form of yeast.

It is not difficult to understand why a macrocytic anemia develops in some patients following partial resection of the stomach. The intrinsic factor which is essential to maturation of the erythrocytes is undoubtedly secreted by the glands in the gastric mucosa. Meulengracht's work<sup>6, 7, 8, 9</sup> indicates that the glands of the pylorus are the most effective in this function, whereas those of the fundus are ineffective and those of the cardiac end of the stomach are only slightly active. He considers also that the active secreting glands are present to some extent in the duodenum. It appears to

be a logical assumption that the development of a macrocytic anemia following operations on the stomach depends almost entirely on how much of the stomach remains following the operation.

The association of this type of anemia with the presence in patients of multiple intestinal anastomoses can readily be explained on the ground that the intestinal contents may pass through only a small portion of the small intestines in such cases and, therefore, the likelihood of absorbing a normal amount of the active principle would be diminished. It is somewhat more difficult to understand why an intestinal stricture or partial obstruction, such as existed in Case 7 of our series should develop a macrocytic anemia, as only a relatively small portion of the small intestine was involved in the pathologic process. A plausible assumption would be that even a localized lesion may in some manner affect the entire intestinal tract in such a way as to destroy or prevent the absorption of the active principle.

The relation of liver disease to the development of macrocytic anemia is thought to be due to the failure of this viscus to function as a storage depot for the active principle which, as a result, cannot be released in an orderly fashion as required to control the maturation of the erythrocytes in the bone marrow. It is assumed in such cases that although the active principle is formed in the stomach and absorbed from the intestine, it cannot be stored in a liver which is extensively damaged and it is lost, therefore, from the body, possibly through the kidneys.

An interesting point for discussion is the length of time required for a macrocytic anemia to develop following resection of the stomach, or after the development of intestinal lesions. Although the information available is incomplete and may not be strictly accurate, all indications are that the anemia does not reach a stage severe enough to produce symptoms for a period of two to five years or longer. The length of time elapsing varies according to several factors. First, it is dependent upon the extent to which the gastric and intestinal function is impaired; it is affected, secondly, by the amount of reserve erythrocyte maturing material which is stored in the liver and perhaps elsewhere in the body. Other conditions which may possibly be of importance are the age of the individual and the presence of infections. These factors are considered because it is known that patients with pernicious anemia who are elderly and those who develop an infection have an increased requirement of the erythrocyte maturing substance. This is known because larger doses of anti-pernicious anemia medication are required to maintain their blood at a normal level. It would seem logical to assume, therefore, that following a gastrectomy, for example, the reserve supply of the active principle would be consumed more rapidly if the patient were elderly or had an active infection, and that on this account a macrocytic anemia would develop more quickly in such a patient.

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# TOLERANCE AND TOXICITY OF INSULIN

## II. WITH FORCED ADMINISTRATION OF CARBOHYDRATE\*

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WHEN insufficient carbohydrate is eaten to protect against insulin, there is naturally a recourse to forced administration of glucose either by stomach or parenterally. In dealing with large doses it is necessary to take account of the toxicity of glucose, though there seems to be no positive information as to whether the injury is entirely physical (osmotic) or whether there is an additional chemical action.

### GLUCOSE CONTROLS

The writer (1913) published the first experiments with prolonged administration of various sugars by various channels, with a view to the diabetogenic influence and also other possible effects of chronic hyperglycemia. Regarding the first, it was established that the digestion or the constitutional strength always breaks down before the pancreatic island function, not only in normal animals but also in those depancreatized to any degree short of diabetes. The dividing line is so sharp that a point is reached where removal of a fraction of a gram of pancreatic tissue makes the animal diabetic and therefore subject to the breaking down of its tolerance with sugar; but without the removal of this final trifle of tissue there is only a moderate reduction shown in assimilation tests and no amount or duration of sugar feeding can bring on diabetes. Other observations made by the writer and by others about that time can now be reinterpreted as evidence that the ordinary death from starvation is due to hypoglycemia, since the feeding or injection of glucose, or the giving of a diet deficient in both protein and calories, at the extreme end of starvation suffices to prolong life by a number of days. The still unsettled question of the effect of long-continued moderate hyperglycemia cannot be answered by administration of glucose to normal animals, because the large doses required break down digestion or general health, perhaps from osmotic causes alone. In order to minimize this factor and also imitate the condition of a continuous circulating excess of an almost unutilized sugar, such as is encountered in diabetes, cane sugar was injected subcutaneously over long periods, the most striking effect being the production of a peculiar obesity combined with imbecile mentality in a cat. This effect upon the nervous

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Reference may be made to the first paper of this series concerning the effect of insulin with spontaneous eating (*New England Jr. Med.*, July 21, 1938).

† With the technical assistance of James H. Rice.



system may be worth further investigation. The writer shares the view of a number of clinicians that a marked excess of blood sugar in diabetic patients is unphysiological and in the course of years may be suspected of responsibility for neuritic pains or general tissue damage, possibly through slight disturbances of hydration or other processes which at present are not accurately understood.

Gigon (1924) fed glucose or levulose to several species of animals for periods up to several months, with the general result of malnutrition. Bouckaert and collaborators (1934) injected rabbits with 200 or 300 c.c. of 10 per cent glucose solution per day, the average result being death in  $3\frac{1}{2}$  days. This was not due to hyperglycemia because it was not preventable by insulin. It was shown by blood analyses to be due to deficiency of circulating chloride, and it was preventable by saline injections.

Large doses of glucose can be given with less osmotic injury intravenously, than subcutaneously or otherwise. Mazzola and Torrey (1933) tested the effect of various single injections from the standpoint of shock. The ideal method, namely continuous intravenous infusion (developed especially by Woodyatt), was used by Butsch (1934). He was thus able to give dogs 3 gm. of glucose per kg. per hour, finding at the end of 36 to 51 hours a sharp break in tolerance as indicated by increased hyperglycemia and glycosuria. There were maximal glycogen deposits, up to 20 per cent in the liver and 2.5 or 3.5 per cent in the muscles. It was possible to continue the injections for 6 to 18 hours longer and demonstrate retention of the same percentages of glycogen; in other words, a break in tolerance in the sense of diabetes was not evident. Jacobs and Colwell (1936) used a continuous slow infusion of 50 per cent glucose in order to give a minimum of surplus water. With injections at rates of 0.7 to 4.5 gm. glucose per kg. per hour, the longest survival was 166 hours. Stained sections showed heavy glycogen but also lesions in various organs. It was concluded that the experiments "show that the continuous administration of glucose even at rates just within the limits of tolerance, that is, not causing glycosuria, is always fatal," while injections at higher rates are more rapidly fatal.

The production of fatal osmotic shock by intraperitoneal injections of either hyper- or hypotonic salt solutions was illustrated by Doménech-Alsina (1932). Gilman (1934) showed similar results with isotonic 5.5 per cent glucose solution, as the result of diffusion of electrolytes out of the blood.

The unavoidability of the osmotic injury with large doses of glucose must be recognized with all methods, since the solution is necessarily either hypertonic before assimilation of the glucose or hypotonic afterward. For example, table 1 shows that 25 gm. glucose in 50 per cent solution by stomach tube is fatal to rabbits, more acutely if the dose is repeated within a few hours. Though the osmotic injury of the strong solution alone is disastrous, other tests have shown severe disturbances from administration of this amount of glucose in any concentration.

TABLE I  
Glucose Controls

Animal Groups	Weight kg.	Treatment	Range of Minimum Blood Sugars mg. %	Range of Red Cell Counts Millions	Result
4 rabbits	2 kg.	25 gm. glucose in 50% solution by stomach tube, once or repeated in 4 hours.	140-760	6.9-12.5	Prostration. Death in 3 hours to 2 days.
2 rabbits	1.8 kg.	3 subcut. injections of 50 c.c. 20% glucose at 4-hour intervals.	120-575	6.1-8.9	Collapse. Death in 18 hours with fever up to 107° F.
1 rabbit	1.7 kg.	3 subcut. injections of 200 c.c. 5% glucose in water, at 4-hour intervals.	122-480	8.3-3.5	Progressive weakness. Death in 15 hours.
2 rabbits	1.5 kg.	3 subcut. injections of 100 c.c. 10% glucose in saline, at 4-hour intervals.	110-360	6.2-7.4	Temporary weakness. Recovery.
5 rabbits	1.5 to 2 kg.	20 to 30 gm. glucose in 10% solution in saline, divided in 2 to 10 subcut. injections daily during fasting.	120-150	7.6-5.3	Death from weakness in 3 to 9 days, while controls fasting without glucose survived.
2 cats	2 kg.	3 injections of 70 c.c. 20% glucose subcut. at 5-hour intervals.	130-540	7.5-13	Weakness. Death within 24 hours.
2 cats	2 kg.	3 injections of 140 c.c. 10% glucose subcut. at 5-hour intervals.	140-370	7.8-6.3	Temporary weakness. Recovery.
4 cats	3.5 to 4 kg.	300 to 450 c.c. 10% glucose solution, divided into 2 to 5 injections subcut., daily during fasting for 10 days.	160-420	6.8-9.3	Survival. Precisely the same loss of weight as controls fasting without glucose, but apparently less strength.

In table 1, it is seen that rabbits and small cats can be killed by the subcutaneous injection of 30 to 40 gm. of glucose in the course of 12 to 15 hours, whether hypertonic (20 per cent) or isotonic (5 per cent) solutions in water are employed. The identical quantity of glucose in 10 per cent solution in saline or Ringer solution was not fatal. On the basis of this and other trials, the last mentioned solution was adopted for routine use.

As the insulin experiments frequently involved administration of considerable glucose to animals during a series of days of fasting, the tables illustrate controls of this kind. Rabbits receiving 20 to 30 gm. daily (notwithstanding division into as many as 10 injections in 24 hours to reduce osmotic shock) died in three to nine days, while the fasting controls survived. Cats, being stronger, survived for 10 days without obvious harm from 30 to 45 gm. glucose per day, but also without benefit. Two points may be noted incidentally. (a) Some of these animals were kept hyperglycemic throughout the entire period, 24 hours every day; the blood

sugars shown range as high as 575 mg., and in experiments not shown it has been temporarily as high as 1500 mg. The essential injury is not due to hyperglycemia, because it occurs under the identical conditions when the blood sugar is reduced with insulin. (b) The strengthening effects of glucose injections, so readily demonstrable in brief trials experimentally and clinically, do not continue with prolonged repetition. According to all available evidence, attempts at parenteral nutrition with glucose during prolonged fasting are harmful rather than helpful. Therefore the benefits of continuous hyperglycemia as imagined by a number of clinicians, on account of glycogen formation, cardiac stimulation, etc., are contrary to the established facts in normal animals. The obvious difference between the endogenous hyperglycemia of diabetes and the induced hyperglycemia in the normal organism leaves the question of harm to the diabetic still open. But as far as any argument can be based upon glucose administration, the proof is positive that nature makes utmost efforts to keep the blood sugar within normal limits and that any prolonged violation of these limits is harmful, not because of the hyperglycemia itself but because of associated processes.

#### GLUCOSE AND INSULIN ADMINISTRATION

Investigation of the specific toxicity of insulin requires the administration of large doses of insulin together with the prevention of hypoglycemia by means of non-fatal doses of glucose.

Crystalline insulin was not used in the present experiments. The kindness of Dr. M. Sahyun of Stearns & Co., in furnishing a supply of the "impurities" of commercial insulin, made possible a number of control tests showing that the results obtained with insulin are not due to foreign substances in the commercial preparation.

Attempts at chronic insulin poisoning were made by Gigon (1924-25), who gave rabbits 10 to 15 units daily and checked convulsions by injections of 10 to 20 c.c. of 20 to 40 per cent glucose. Death occurred in 4 to 23 days. The need for the glucose injections is not clear, since rabbits readily tolerate such small insulin doses with spontaneous eating. Likewise the fatal outcome was probably due to malnutrition rather than to any direct effect of the insulin. Also Dünner, Ostertag and Thannhauser (1933) used dogs, rabbits and guinea-pigs. Their "small" doses were 2 to 4 units, but the amount of the "large" doses is not mentioned. After nervous symptoms, depression and malnutrition for eight weeks a dog was found unconscious with normal blood sugar. Examinations after death showed various organic lesions, glycogen-free liver and glycogen-poor muscles. On the other hand Long and Bischoff (1929) started rabbits at three months of age on 6 to 14 units of insulin daily, and in observations of more than six weeks found nothing more than a failure to gain weight beyond the controls. From this and other work it may be concluded that a state of chronic insulin poisoning has never been demonstrated.

Investigation of the toxicity of large doses in acute experiments was

attempted by Loeb, Nichols and Paige, who, using 2 kg. rabbits, injected 75 units of insulin per kg. intravenously and repeated the same in four hours. According to internal evidence in the paper, these young authors carried out the actual procedures accurately but fell into certain errors in planning their experiments. Three of such errors may be cited: (1) The observations were terminated  $7\frac{1}{2}$  hours after the first,  $3\frac{1}{2}$  hours after the second insulin dose. The principal effects, namely the delayed ones, were thus missed entirely. Even with reference to their primary problem, namely the possible toxicity of high insulin doses in diabetic coma, there was no reason to assume that the treatment or the results are finished within an 8-hour day. (2) On the assumption that their supposedly huge dosage must be balanced by equally huge amounts of glucose, they gave 12 gm. of glucose per kg. in 50 per cent solution by stomach tube after each insulin injection, without any control experiments to ascertain whether such a dosage is in itself not fatal on account of both quantity and concentration, and whether much smaller amounts would not suffice to balance the insulin. (3) After only  $7\frac{1}{2}$  hours some rabbits were dead, many others were dangerously weak; all were then killed after this insufficient period of observation, and the conclusion was drawn that insulin is non-toxic. The uncritical acceptance of this conclusion seems to constitute the only basis for the prevailing view of the non-toxicity of insulin apart from hypoglycemia.

#### EXPERIMENTS.—PARENTERAL GLUCOSE WITH INSULIN

##### 1. EFFICIENCY

In general, it is possible even with the most enormous insulin doses to save an animal by a small subcutaneous injection of glucose at the very beginning of convulsions or collapse, the absorption being rapid enough to halt the attack. This was the method used routinely, supplemented if necessary by intramuscular and intraperitoneal injections.

Intravenous injections, being the most rapid and precise in effects, permit of a slight saving of glucose in comparison with the other methods. A convulsion resulting from 50 units of insulin in a rabbit can be checked with as little as 0.2 to 0.4 gm. of glucose by vein; such protection may last from a few minutes to half an hour, depending upon the stage of the process. A rabbit was completely protected against a subcutaneous dose of 50 units by means of repeated small intravenous injections totalling 5.9 gm. of glucose in 10 hours.

##### 2. INSUFFICIENT AND EXCESSIVE GLUCOSE

It is well known that animals can sometimes remain in serious hypoglycemia for a considerable period without violent seizures. When convulsions or collapse finally appear, glucose may fail to save life, and such a death can be attributed to insufficiency of glucose from an early stage. The temptation therefore exists to go to the opposite extreme by supplying

TABLE II  
Rats—Insulin with Parenteral Glucose Injections

No. of animals	Weight gm.	Insulin units subcutaneously	Hours before first reaction	Glucose in first 6 hrs. gm.	Glucose in second 6 hrs. gm.	Glucose in second 12 hrs. gm.	Total glucose required gm.	Total hours of treatment	Final blood sugar mg. %	Result
6	130-240	10-30	2½-4	0.6-0.9	0.5-0.8	0	1.2-1.6	8-12	60-110	Comfortable; lived
8	120-225	40-80	2½-3	0.9-1.3	0.7-1.2	0.5-0.9	1.9-3.3	16-24	52-140	Slight depression; lived
6	110-220	100	2-3½	0.9-1.5	1.1-1.4	0.4-1.3	2.6-4.0	15-24	78-190	Slight depression; lived
6	125-240	150	1½-2½	1.4-1.8	1.2-1.6	1.0-1.5	3.5-4.6	20-26	56-210	Depression; lived
4	110-200	200	2-2½	2.0-4.0	1.8-2.8	1.6-2.0	5.0-6.6	18-30	48-181	Weakness; lived
5	140-320	250	1½-3	0.4-2.8	0.4-3.0	2.3-3.5	2.5-12.4	21-42	40-234	Weakness; dyspnea, death
1	110	300	—	2.5	1.8	—	4.3	10	256	Rapid weakness; death
1	270	325	3	0.5	1.0	1.0	3.5	20	90	Recovered
1	300	400	2½	1.3	2.0	1.0	7.3	34		Weakness, dyspnea, death
1	190	800	1½	1.5	1.0	0.5	3.0	15		Weakness, dyspnea, death
		Intra-venously								
3	120-215	10-30	2-3½	0.4-0.8	0	0	0.4-0.8	6	52-76	Comfortable; lived
5	115-210	40-80	1½-2½	0.5-1.2	0.9-1.2	0-0.4	1.5-2.7	12-15	81-157	Slight depression; lived
4	110-200	100	1½-2½	0.9-1.5	0.8-1.1	0.8-1.4	2.6-3.8	16-20	42-198	Three died, one survived
3	120-180	150	1½-2½	1.3-1.7	1.4-2.0	0.5-1.0	3.4-4.6	13-17	38-250	Weakness, dyspnea, death

TABLE III  
Other Species—Insulin with Parenteral Glucose Injections

Animals	Weight kg.	Insulin units	Hours before first reaction	Total glucose required	Hours of treatment	Initial erythrocyte count. Millions	Final erythrocyte count. Millions	Final blood sugar mg. %	Result
4 rabbits	1.8-2.2	Subcutaneously 50	2½-3½	10-13	9-12	7.7	9.8	62-98	Comfortable; lived
2 rabbits	2	100	2½-3	17-21	11-15	6.3	7.3	75-194	Depression; lived
4 rabbits	1.9-2.3	150	1½-2½	21-25	16-24	6.9	—	88-165	2 lived; 2 died
2 rabbits	2.0-2.1	150 repeated in 4 hrs.	1½-2	98-106	74-100	—	2.2	180-224	Weakness, dyspnea, death. Trace of glycogen in liver, heart, skeletal muscles
6 rabbits	2.0-2.3	200	1½-3	28-42	16-36	8.1	4.0	115-288	1 lived, 5 died
6 rabbits	2.0-2.4	250	1½-3½	21-44	19-29	—	—	120-214	5 died under treatment; 1 died in sudden convulsions 12 hrs. after last glucose injection
3 rabbits	2.3-2.6	300	1½-1½	17-35	10-34	—	—	—	2 died under treatment; 1 died in convulsions 20 hrs. after last glucose injection
5 rabbits	1.7-2.1	Intravenously 50-100	1-1½	7-12	7-9	—	—	52-184	Slight depression; lived
4 rabbits	1.8-2.3	150	1½-1½	8-15	10-14	7.9	6.1	79-194	Depression; lived
4 rabbits	2.0-2.3	150 repeated in 4 hrs.	1-1½	13-24	9-22	7.0-8.0	3.1-5.8	103-360	2 lived, 2 died (liver glycogen-free)
2 rabbits	2.1-2.3	150 repeated in 4 hrs. 2nd day	¾-1	18-26	13-17	4.1	2.8	190-235	Weakness, dyspnea, death
3 rabbits	2.0-2.6	200	1½-1½	8-18	7-16	—	—	84-600	1 lived, 2 died
4 cats	3.0-4.0	Subcutaneously 50-100	4-5½	7-9	8-10	7.6	9.2	52-170	Slight depression; lived
5 cats	2.5-3.5	200-500	3½-4½	15-24	18-26	—	—	87-320	Weakness; lived
3 cats	2.2-3.2	800	3½-5	16-28	28-44	—	—	70-1400	Weakness; lived
5 cats	2.8-4.0	1000	2½-4½	8-20	16-21	7.9	11.3	66-484	4 lived; 1 died
4 cats	3-3.8	1200-1500	2-3½	12-22	14-22	—	—	107-208	Died
1 dog	10	2500	3½	190 (114 by vein and 76 subcutaneously)	55	5.3	3.1	180	Progressive weakness, dyspnea, minor and major spasms, death

glucose liberally from the outset, so as to prevent all symptoms from beginning to end. With the largest insulin doses, involving the longest treatment, this method results in killing some animals with glucose, when those which receive less sugar survive. In general, it has seemed best to await the first signs of a beginning attack and then check it by a small subcutaneous injection of 10 per cent glucose in saline or Ringer solution (usually 2 to 5 c.c. for rats, 10 to 20 c.c. for rabbits or cats). A long series of such brief convulsions seems to be not dangerous, even when continued through several days. At the same time numerous quick blood sugar analyses are necessary, for information concerning unsuspected hypoglycemia or the dyspnea and convulsions which sometimes occur with marked hyperglycemia.

Deaths resulting either from hypoglycemia or from excessive glucose are not instructive for the present problem. Accordingly, many animals were not suitable for inclusion in tables 2 and 3. The data in the vertical columns of these tables will now be discussed in succession.

### 3. ANIMALS. WEIGHT

In only a few trials were matched animals or litter-mates used. Many were used immediately after being received, and others after long stay in the laboratory. Animals of similar size and apparent strength frequently differ in their response to insulin doses, for unknown reasons. There is not even a consistent relationship with the body weight. The factor of strength, however, deserves emphasis. Animals weak or sick from any cause are markedly subnormal in insulin tolerance.

### 4. INSULIN DOSAGE

Rats are the only species thus far tested having a higher insulin tolerance with spontaneous eating than with parenteral injections.\* Incidentally, it should be understood that mixed programs are possible, and rats which have stopped eating with huge insulin doses may sometimes be revived by parenteral injections, and then resume eating and survive.

With insulin and glucose both given subcutaneously, the tolerance limit of ordinary sized rats seems to be 200 units, with which a majority died. One large animal survived after 325 units. With as little as 150 units, there were two deaths out of four, in addition to a larger number from hypoglycemic accidents not tabulated.

The high mortality of rats from insulin given intravenously, beginning at 100 units and becoming 100 per cent at 150 units, is probably due to accidental or extraneous factors; such as impurities or the larger volume (U 40 commercial insulin being used). It was not connected with any special difficulty of keeping up the blood sugar level, and it was contrary to the results in larger species.

The larger species survive far higher insulin doses with parenteral glucose injections than with spontaneous eating.

\* Work to be published subsequently indicates that this is true also for the guinea pig.

Following the plan of Loeb et al., it is found that rabbits can survive 150 units of insulin intravenously, and at least some of them can survive this dose repeated in four hours, provided they are not killed by excess of glucose. But as regards application to diabetic therapy, which in acidosis often requires high insulin on more than one day, it must be noted that the above dosage is fatal to rabbits when repeated on a second day. Also in practice insulin is generally administered subcutaneously rather than intravenously, and the subcutaneous injection of 150 units repeated in four hours is fatal to rabbits.

Apparently the upper limit of insulin tolerance in rabbits is from 150 to 250 units either subcutaneously or intravenously, in other words about equal in absolute values to the tolerance of rats. The intravenous injections are

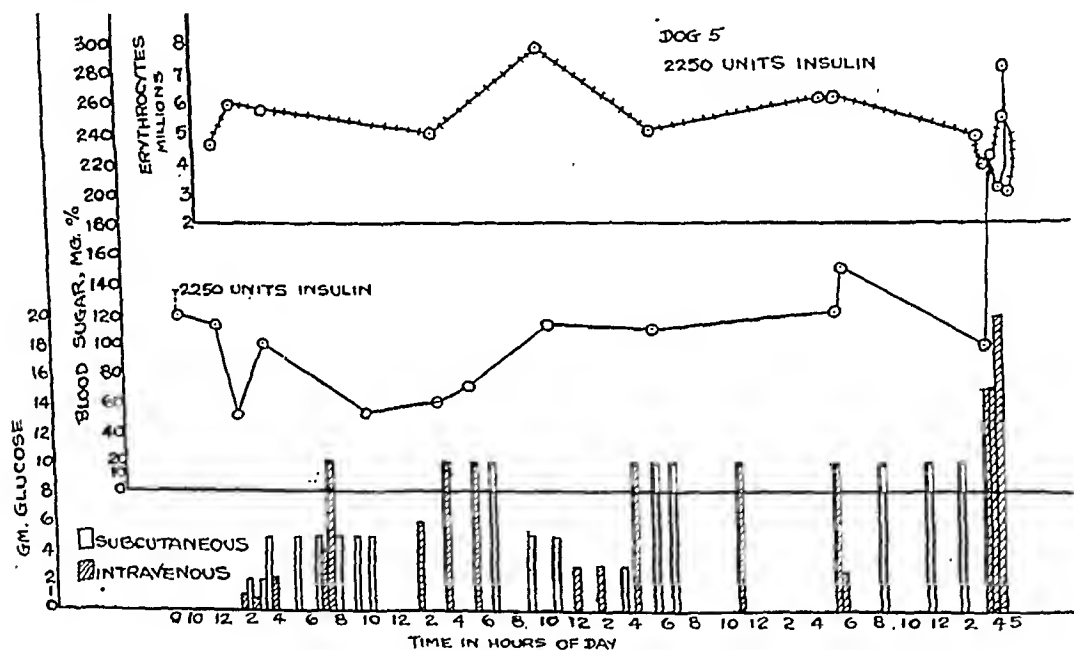


FIG. 1.

less dangerous (as illustrated particularly by the ability to repeat the 150-unit dose intravenously but not subcutaneously) but also less powerful as judged by the briefer duration and the smaller amount of glucose required for antidoting.

Cats of average size proved able to tolerate 1,000 to 1,200 units subcutaneously but not 1,400 units or higher doses.

Several observations on dogs may be described at this point, as follows. The 10 kg. animal in table 4 is represented in greater detail in figure 1, which shows in particular that the death could not be attributed to hypoglycemia.

The 14 kg. animal depicted in figure 2 survived an insulin dose of 2,000 units (in the Psychiatric Institute). Here the toxicity of glucose was minimized by the use of minimal quantities. No attention was paid to hypo-



TABLE IV  
Food and Glucose Administration after Insulin Injections in Rabbits

Rabbit No.	Insulin subcut. units	Food by stomach		Glucose subcut. gm.	Duration of treatment hours	Result
		Voluntary	By tube			
1	250	130 gm. lettuce, 10 gm. bread, 10 gm. oats	50 c.c. milk, 100 c.c. 10% glucose	20	40	Progressive weakness; death.
2	250	25 gm. bread	300 c.c. milk	2	24	Recovery. Appeared well at end of treatment; died later when unwatched, presumably from delayed hypoglycemia.
3	250	—	260 c.c. 10% glucose	21	45	
4	250	—	350 c.c. 10% glucose	2	14	Fasting afterward, remained symptom-free.
5	350	20 gm. carrots, 5 gm. oats	100 c.c. 10% glucose	22	32	Moderately weak at end of treatment; died later when unwatched.
6	400	—	300 c.c. milk, 50 c.c. 10% glucose	8	19	Fasting after treatment, symptom-free. Recovery.

glycemia, except that whenever a convulsion began 10 gm. of glucose were immediately injected intravenously. Although the last of these active seizures occurred 30 hours after the insulin injection, it is noticeable that distinct hypoglycemia lasted into the third day. Only on the fourth day the blood sugar rose to a level slightly above normal for a fasting animal.

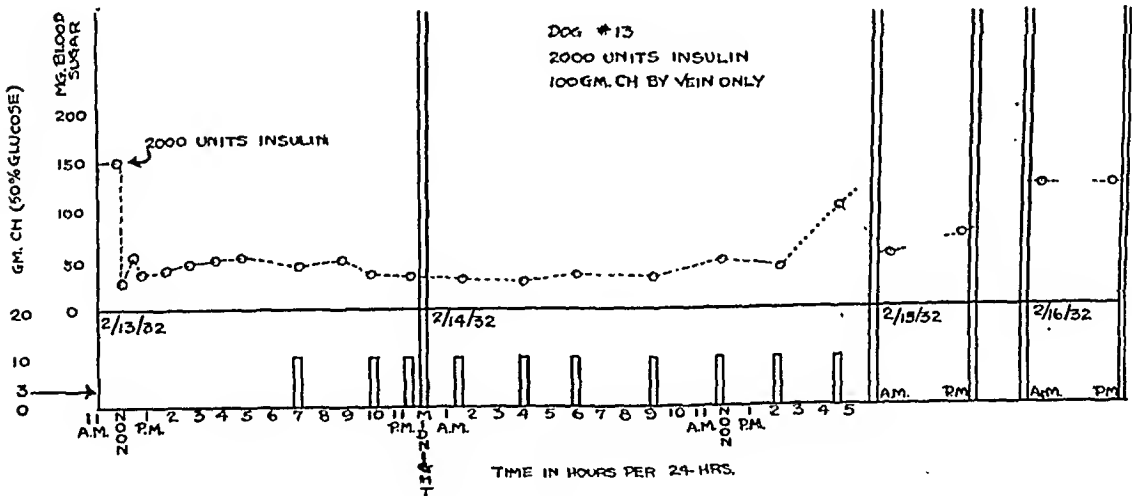


FIG. 2.

A third experiment was carried out on a 4 kg. dog with the coöperation of Drs. Barkley, Blum, Ferraioli, Kastle, Kemp, Saxe and Shetter of the Polyclinic Hospital staff. Instead of the insulin being given in a single huge injection, it was begun with a dose of 400 units followed by injections every hour or two, diminishing gradually to 100 units, then 50 units and

finally 20 units each, all subcutaneously, so as to maintain a constant inflow rather than a single sudden flood of insulin. The total time from the first injection to death was 57 hours. In this way the insulin dosage amounted to 1900 units in the first 24 hours, 800 units in the second 24 hours, and 100 units in the remaining 9 hours, making a total of 2800 units, or 700 units per kg. Also a continuous intravenous infusion of 10 per cent glucose in Ringer solution was given, beginning at 100 c.c. per hour and reduced as needed, down to as low as 50 c.c. per hour during much of the time. Also during two periods totalling 14 hours the tube was withdrawn from the vein altogether and the blood sugar was kept up by small subcutaneous injections. Frequent analyses proved that the blood sugar was thus maintained between the limits of 110 and 360 mg., with a single exception of 600 mg. According to the experience of Butsch, also Jacobs and Colwell, such glucose injections are non-fatal, and the death must therefore be attributed to an action of the massive insulin dose, other than hypoglycemia.

#### 5. INTERVAL BEFORE FIRST REACTION

Whether animals are fed to within a few hours of beginning the experiment, or whether they fast for various periods up to 24 hours, seems to make little difference in the survival with large insulin doses. It necessarily makes a difference in the time of onset of hypoglycemia and its symptoms. Some of the irregularities in this interval are explained by the differences in preparation. It is also realized that the active attacks are not an infallible index of the hypoglycemia. Nevertheless there were enough comparisons under controlled conditions to confirm the irregular response of individual animals described by previous writers. In general, the interval before the first symptoms is shortened with increasing dosage but the individual exceptions still occur, and in particular the degree of shortening of the interval is by no means in proportion to the degree of increase of dosage; i.e., sugar consumption and perhaps also glycogenolysis are not very greatly accelerated by the huge doses. Also the shortening of the interval with intravenous insulin administration is much less than might be anticipated.

#### 6. AMOUNT OF GLUCOSE REQUIRED

The glucose utilization shown in the successive periods evidently maintained a fairly level plateau until the surplus insulin was nearly used up. In the comparison of subcutaneous and intravenous insulin administration, the figures shown for the rats are probably misleading, because most of these animals were overdosed with glucose in the attempt to prevent the high mortality. The rabbits prove conclusively that insulin is less efficient, in the sense that it can be antidoted with much less glucose, when it is given intravenously than when it is given subcutaneously.

The results of these experiments, and also of others in which such large quantities of glucose were given as to prove fatal, reveal no change whatever in the duration of the insulin effect corresponding to any differences in the glucose supply.

## 7. DURATION OF HYPERINSULINISM

The hours of treatment are counted from the time of the insulin dose to the time of the last glucose injection. In certain instances the disturbance of the time factor by early deaths from large insulin doses must be noticed. In general the most striking point is the trivial increase of rate of glucose consumption, in contrast to the great lengthening of time,\* which predominantly governs the amount of glucose used. An argument against insulin-glucose ratios is found in the fact that they thus depend not on an intensity of reaction between the two substances but chiefly upon the length of time insulin happens to be retained in the body. With maximum doses this time may be surprisingly long; e.g., 55 hours in a dog after a single insulin injection, and 100 hours in a rabbit after two injections four hours apart. Theoretically, it would seem possible to extend this time indefinitely, if only the animal could withstand the intoxication from either insulin or glucose.

The inferiority of intravenous as compared with subcutaneous insulin administration, as shown particularly in rabbits (the effect being much shorter, and not particularly more intense while it lasts) warrants two inferences: (a) A large part of the intravenous flood of insulin is evidently disposed of in some purely wasteful manner, without benefit as measured by glucose consumption. (b) A part of this insulin also is retained in the tissues, as proved by the recurrence of hypoglycemic attacks for the number of hours shown. Therefore, though the method of continuous intravenous infusion may be ideal under the right conditions, if it is used for very large doses it must encounter these same factors of waste and storage, and accordingly proof will be necessary whether it is superior, equal or inferior to the subcutaneous method.

The production of genuine and prolonged hyperinsulinism is readily demonstrated in amputation experiments. For example, if a cat is given an injection of 1000 or 1200 units of insulin near one ankle, and if a mid-thigh amputation is performed 12 to 24 hours later, the general condition and progress and the amount of glucose required remain essentially unchanged. Such animals in fact show a slightly greater insulin effect, as judged by either intensity or duration of hypoglycemia, because of the added element of shock. Such experiments leave no doubt that the essential condition is not a mere delay of absorption, but that a state of true constitutional hyperinsulinism can persist for 48 hours or longer following a single subcutaneous injection.

## 8. ERYTHROCYTE COUNTS

To form some idea of the blood concentration, numerous red cell counts were made. Typical results in single individuals of the larger species are shown for various insulin doses in the table. A concentration of the blood

\* Likewise with small insulin doses, Zucker and Berg (Am. Jr. Physiol., 1937, cxix, 531-538) found that increased dosage increases the duration rather than the degree of hypoglycemia.

by insulin is established by agreement of most authors (literature by Hill and Howitt). The changes shown in table 4, together with far more numerous examples of marked hydremia in rats not tabulated, seem to be chiefly the result of the large injections of glucose with insulin. The interesting question whether there are any consistent differences in blood concentration with identical glucose injections with and without the large insulin doses was not settled.

### 9. FINAL BLOOD SUGAR FIGURES

The great majority of blood sugar analyses cannot be reproduced. The final figures shown vary chiefly according as they were taken soon or late after a glucose injection. Their only real importance is in showing that animals were not hypoglycemic at death. The earlier unpublished part of each record must be understood as showing likewise that there was no preceding hypoglycemia sufficient to account for the fatality.

It should also be noticed that the time shown in the tables does not represent the true total duration of hyperinsulinism, but only the period of sufficient severity to require glucose injections. Actually, all animals subsequently pass through a stage as illustrated in figure 2, namely a period of perhaps 24 hours following the last glucose injection, characterized by slight general depression and subnormal blood sugar levels, e.g. 50 to 70 mg. With this evidence it is readily proved that a single large subcutaneous injection can produce a state of hyperinsulinism lasting two to three days.

### 10. RESULTS

In all species, the results of the largest insulin doses were anorexia, depression, weakness, dyspnea, convulsions and death. Hydremia was the rule with glucose injections (not hypertonic). The body temperature commonly became subnormal, especially in rats. Some rabbits and a smaller number of cats showed fever, up to a maximum of 108° F., probably attributable to osmotic effects of the glucose solutions.

In view of the prolongation of time without much increase of intensity of glucose consumption, it might be argued that a large excess of insulin merely lies idle. On the contrary, it appears that (*a*) the large insulin doses produce symptoms of malaise, anorexia, etc. as previously mentioned, increasing as the doses increase, beginning before the hypoglycemia and mostly continuing in spite of glucose injections; (*b*) the increasing severity of this same condition seems to be responsible for slow or sudden death, regardless of the blood sugar if the insulin dose is high enough. At the same time the danger of sudden hypoglycemic death, with a brief convulsion or only one expiratory cry, must be recognized, notwithstanding the apparently slight acceleration of glucose consumption by the large doses. With a few units an animal may have repeated convulsions with weak or unconscious periods between, the available reserves of traces of glycogen, lactic acid, etc.

apparently sufficing as partial antidotes; but doses running into hundreds of units allow no such respite and often demand instantaneous treatment.

### 11. EPINEPHRINE

Extra stimulation of epinephrine discharge may be suggested in connection with the results of large insulin doses. It has not been feasible to attempt physiological tests or even to investigate possible exhaustion of the adrenal medulla. Since such small amounts as 0.2 to 0.4 gm. of glucose were found to ward off hypoglycemic crises in rabbits, it appeared conceivable that small repeated epinephrine injections might likewise protect against large doses of insulin, or, if glycogen were lacking, that they might reinforce the effect of glucose injections. A few such trials of epinephrine subcutaneously or intraperitoneally failed. A brief reviving effect is obtainable at first, but subsequently the epinephrine appears unable to save life either by itself or by reducing the necessary quantity of glucose.

With reference to the possible suggestion that the toxicity of insulin is due to increased discharge of endogenous epinephrine, the results as far as they could be judged superficially seemed to indicate that the injection of additional epinephrine was helpful rather than harmful.

### 12. FORCED FEEDING

As previously mentioned, the advantage of rats with large insulin doses is that they continue to eat while other species lose appetite. Accordingly, trials were made with forced feeding in a species which does not vomit, namely the rabbit. As shown in table 5, it proved actually possible to save life in this way with insulin doses which are fatal when only parenteral glucose injections are used to prevent hypoglycemia. A toxic action of the insulin was still demonstrated by the anorexia itself and by various degrees of weakness. Inhibition of digestion or absorption also seemed to be indicated by the inability to prevent hypoglycemic attacks by stomach feeding alone and the necessity of depending partly upon parenteral glucose injections. Nevertheless there was enough retention of function to prevent any extreme distention or diarrhea and to reduce greatly the amount of glucose needed parenterally.

A careful study was made by parallel experiments in both rabbits and rats, of which details are omitted, concerning a possible specific influence of intestinal digestion or absorption. This touches the well-known questions of antagonism between internal and external secretions of the pancreas, the possible liberation of an anti-insulin hormone during digestion, the special rôle of the liver, etc. These experiments included the administration of equivalent quantities of glucose subcutaneously, intraperitoneally, or by stomach, and pure starch or bread by stomach. It was definitely ascertained that the route of administration or the digestive process has no influence whatever upon either the degree or the duration of the effect, aside from differences in the time of absorption. (Cf. figure 3 in paper no. 1.)

Evidently, the diminished toxicity of insulin when either glucose or starch is fed is due to avoidance of the injury of parenteral glucose injections. The rather difficult question of the respective influence of insulin and glucose can be conveniently studied in rats, though the conditions in other species are similar. If certain rats receive large insulin doses together with a sufficient series of glucose injections to prevent hypoglycemia, while control rats receive the same glucose without insulin, a casual observer can easily distinguish one group from the other, because the insulin animals are humped up, with fur fluffed; they are less lively, have lower temperature, and appear more swollen as if the injected fluid were more slowly absorbed. They may thus die while the controls survive. But if the quantity of injected glucose is sufficiently increased in the controls, the precise appearances of the insulin rats are reproduced and death occurs similarly.

Two possible explanations therefore suggest themselves: (*a*) that the injury from injected glucose is not only physical (osmotic) but also chemical, perhaps through formation of toxic substances as supposed by Fischler, and that this identical intoxication can result from sufficiently large injections of glucose alone or from smaller quantities of glucose under the intensifying action of insulin; (*b*) that the injury from parenterally injected glucose consists solely in osmotic shock, while overdosage of insulin sensitizes the organism to every form of shock. The latter explanation is favored by the lessened injury with glucose feeding, by the easy death of weak animals from insulin, and by the easily demonstrable sensitiveness of insulin-treated animals to surgical and other shock.

A distinction between insulin intoxication and glucose intoxication seems to be afforded also by the autopsy findings. As far as a conclusion can be based upon the few analyses which were possible under the conditions (table 4), animals dying from glucose alone are glycogen-rich while those dying from high insulin dosage even without hypoglycemia are nearly or completely glycogen-free.

### CONCLUSIONS

1. Parenteral glucose injections produce a beneficial stimulation only with brief administration, and when continued over a long period become harmful or fatal.

2. The tolerance of several species for insulin in conjunction with parenteral glucose injections has been established. Insulin can kill through the carbohydrate metabolism in two ways: (*a*) by hypoglycemia; (*b*) by creating a demand for fatal quantities of glucose.

3. The general conclusions of the preceding paper are confirmed in the experiments with parenteral glucose. The duration of hyperinsulinism is greatly increased with increased dosage, to limits beyond 48 hours for a single subcutaneous injection. On the other hand, the rate of glucose consumption is not increased in proportion to the insulin dose, also the time

required for using up the insulin is not altered by changes in the glucose supply. Glucose-insulin ratios must be regarded as merely imaginary or accidental relationships, because there has never been any evidence of an interaction of glucose and insulin in which the two are mutually and quantitatively consumed.

4. Intravenous injections are much less powerful than subcutaneous injections of insulin, inasmuch as there is no important difference in the intensity of effect as judged by the rate of glucose consumption and the duration of this effect is much shorter; also their toxicity is far less. A large waste of insulin is evident.

5. Large doses of insulin can be antidoted by a series of very small glucose injections, but they cannot be antidoted by a series of epinephrine injections.

6. The most efficient protection is afforded by a combination of enteral and parenteral carbohydrate administration, not because of any specific influence of intestinal digestion or absorption, but only because of avoidance of some of the injury resulting from parenteral injections alone.

7. The excess of insulin above that which produces the maximum effect upon the rate of glucose consumption does not lie idle and ineffective. Absorption is demonstrated by amputation experiments, and by the marked intoxication occurring before the carbohydrate reserves have been seriously depleted or in spite of glucose injections which prevent hypoglycemia. The toxic symptoms resemble those produced by glucose injections alone, but distinctions are apparent; namely, (*a*) in hyperinsulinism the symptoms occur with smaller glucose injections than in the controls; (*b*) according to a few analyses, glycogen is abundant in the controls dying from glucose alone but is nearly or completely absent in hyperinsulinism. The only significance is believed to lie in the fact that hyperinsulinism creates sensitiveness to the osmotic shock of glucose injections and all other forms of shock.

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# PSYCHOTHERAPY, WITH SPECIAL REFERENCE TO THE USE OF HYPNOSIS \*

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PSYCHOTHERAPY in some form or other is used by every physician, and although the surgeon may use it only occasionally, the internist uses it constantly, even though he may not think of it as such. He may consider psychotherapy as persuasion, readjustment, reëducation, psychoanalysis, hypnosis, suggestion, or even bluff. Every physician admits the use of placebos, and although he may dismiss the case as purely functional, imaginative, hypochondriac, neurotic, or just faking, he usually realizes that the patient wants something done for him and so he gives a prescription, an injection, an electric treatment, or a bottle of medicine with the hope that the patient will have the faith that it will cure him. This faith in the physician and his treatment is highly fundamental, because many patients are treated by the best trained physicians and are never cured, while others get better even without treatment.

In many cases the type of personality with which one has to deal, the stubborn nature of the condition whether physical or mental, or the existing insuperable environmental factors make the treatment, not to mention the cure, almost impossible. In other words, the case may be inoperable. But, if the patients' symptoms are not too fixed and he sincerely coöperates with the physician, then the symptoms may be removed without difficulty, and the distorted personality corrected. It is unfortunate that as a general rule a somatic disorder is categorically diagnosed without regard to the underlying personality, and the treatment instituted is purely physical. On the other hand, if symptoms arise that are obviously psychogenic and are apt to be troublesome, the physician may refer the patient to a specialist to get him off his hands, or he may dismiss him with an uncomplimentary remark and so drive him away from qualified physicians and force him to become the support of some quack or cult. Every physician should remember that properly applied psychotherapy in the form of intelligent management will likely bring about a fair degree of adjustment in the majority of cases, and a true cure is not uncommon.

If the physician finds that the symptoms that he is called to deal with are mostly mental, he should remember that it is unwise for him to tell the patient that there is nothing wrong or that it is all imagination. He may justly resent the one as false and the other as insulting. The fact is, that a functional symptom is just as real as an organic one. Most patients would rather have an organic ailment and be done with it than one which generally gets scant sympathy from the family and indifferent attention

\* Read at the New York meeting of the American College of Physicians, April 8, 1938.



from the physician. To insinuate that a patient makes believe, or that his complaints are not real to him, is a serious psychotherapeutic error which will lose the trust and confidence of the patient. He will at once attribute this to the ignorance or lack of understanding of the physician. It is just as grave an error to pat the patient on the back and tell him that he should forget his anxiety, phobia, or compulsion.

The first necessity is for the physician to develop the patient's confidence or establish rapport, by taking the patient, or at least his complaint, very seriously. This is best accomplished by obtaining, as meticulously as possible, a medical and social history and making a very complete and thorough physical examination. No snap diagnosis should be made, and no conjectures should be expressed, but if no physical ailment is found the patient can be repeatedly assured on that score, and the normal anatomy and physiology explained to him. On the other hand, he should be told that a psychic, nervous or mental condition is just as real as a physical one, and that fright, shock, anxiety, or personal conflict may cause nervousness and create definite symptoms. As an example, he can be told that the sweat that comes out on the palms of the hands when a person is frightened is just as real as the sweat that comes out after exercise: or that the diarrhea caused by anxiety is just as real as the diarrhea caused by a dose of salts.

The physician must be careful to use language that will be understood, as most persons, and especially neurotics, have a special capacity to misinterpret what is said to them, and may even conclude that if the physician uses the word mental, he has diagnosed them as "insane." Most people are afraid of going "insane," for that means commitment to a state hospital. On the other hand, although the physician should be understandingly sympathetic, he must never become facetious about the illness or descend to intimacy or levity, but must preserve a sense of dignity and convey the impression that he possesses sound medical knowledge and good insight into the problems of human behavior.

A physician may not realize that when the patient comes to him for help he is willing to bare his very soul if necessary. Every word and action of the physician is seized upon, and without realizing it, the patient develops a confidence that is akin to infatuation or love. If the physician allows any advances or takes any liberties he creates an emotional situation that may lead to grave complications. The so-called "bedside manner" of some physicians should be absolutely discontinued, such as putting an arm around the waist, patting the hand, or as I have observed, even kissing the patient or holding the hand during the conversation. This makes the relationship between the patient and the doctor a personal matter, and will block any constructive psychotherapy. Personal relationships are subject to censorship, and if there is a personal feeling between the patient and the physician, the patient will be reticent about talking about matters that may affect this relationship and yet which need to be brought to light if a readjustment is to be brought about. On the other hand, the physician

should not give the impression that he is a judge, set above the patient, but is a friend who feels what the patient has done is neither good nor bad, moral nor immoral, beautiful nor ugly, decent nor indecent, but the result of circumstances.

The physician should certainly not give the impression that he is a wizard, set apart from the world, who can cause a cure by a wave of a magic wand. Psychotherapy is not a confessional, although a confidential talk may relieve many emotional tensions. It is not a sermon, nor a lecture, nor "psychologizing," nor moralizing, nor "psyching," nor does the physician bewilder the patient with stereotyped symbols, for these may only tend to confuse and befog the problem. Above all, the physician should be a human individual with understanding, self-control and common sense.

It is quite obvious that if some organic defect is found, an attempt should be made to correct it if possible. Unless the organic condition is paramount it is unwise to overemphasize it, for fear that the patient may seize upon some minor or even major physical symptom and continue in his persistent refusal to face the more important problem of getting better. Sometime ago, a young man came into my office very much upset because he had been emphatically told that he needed an appendectomy without delay. In fact the physician who had seen him had told him that he could see in the fluoroscope that the appendix was in very bad condition and about to rupture. The young man wanted to know if he could stand an operation nervously. A thorough physical examination clearly showed that the appendix was not involved, and that the abdominal discomfort was due to intestinal indigestion. The patient was calmed down, put on a corrective diet, and his abdominal pain cleared up without delay. Nevertheless, the seeds of uncertainty had been placed in his mind, and in spite of psychotherapy, he persisted in shopping among the specialists until he found one who would remove the appendix for a consideration. Yet, the personality has not been corrected, and this is the first of a series of operations that undoubtedly the young man will undergo in his attempt to justify his neurotic behavior. The object of psychotherapy, the practice of which literally begins the moment the patient crosses the threshold of the doctor's office, is to influence the problems of personality, while the detailed physical examinations, in addition to giving an understanding of the organic make-up under consideration, in itself becomes a psychotherapeutic measure.

The physical examination may lead one to the conclusion that some operative measure, medication, hypodermic injection, exercise, gymnastics, massage, electricity, baths, rest cure, or what not, may be needed, but suggestion will play a very important part in these procedures. Perhaps the removal of a chronic appendix, or a fibroid, may help to remove the abdominal pain. Certainly foci of infection should be properly treated and complicating organic affections attended to, but one cannot insist too often on the fact that no personality problem was ever cured by mechanical means. Neither surgery, hypodermic or other medication, nor any form of physio-

therapy, will cure a deep-seated phobia, or dispel a paralyzing obsession. Operations, glandular therapy and other medication, are many times curative and necessary, but great numbers of patients have been invalidated and their neurotic symptoms made permanently inaccessible by the unwise application of these methods.

Because of high-pressure salesmanship by drug firms, and lack of understanding on the part of the physicians, narcotics and hypnotics are indiscriminately dispensed or prescribed. In general it may be said that the less medication and the more psychotherapy, the better, although with inaccessible patients often all one can do is to prescribe some placebo. But even so, the effectiveness of most prescriptions is in direct proportion to the amount of suggestion they embody.

There is no objection to a patient taking a trip, a brief sojourn at a health resort, hospital, sanatorium, or spa, but obviously the virtue of such treatment resides in the efficacy of temporary removal from the aggravating environment. Since personality problems are rooted in inner and outer conflicts, and the patient takes the former with him, and must return to the latter, it is highly probable that no permanent benefit will be derived from temporary or even prolonged sojourn away from home.

Physicians are frequently confronted with the results of pilgrimages to places where faith or miracle cures are performed, and there is no doubt that isolated and spectacular cases of religious hysterics with outspoken conversion phenomena have been helped. But these cases can all be explained by the effects of suggestion, and most other cases go unhelped.

It is necessary to remember that many environmental factors are beyond the ability of either the patient or the physician to cope with, and yet it is obvious that these factors may be the cause of symptoms, although the genesis of functional symptoms is not one of logic or intelligence. The subjective, emotionally tinged, unconscious, is at the back of these symptoms, and besides the need for adjusting the personality to the environment, it is well to bear in mind that mentally created symptoms are in themselves a compromise attempt at adjustment. These symptoms may have been unconsciously grafted on to the personality pattern, during childhood or later years, through the method of suggestion.

Without realizing the source of these symptoms, the physician may attempt to reason them away through persuasion. Persuasion denotes an appeal to moral sentiments. The attempt is consciously to resolve conflicts and reintegrate the personality. Obviously this implies an intellectualistic concept of the etiology of neuroses, while actually, functional symptoms are rooted in deep-seated unconscious conflict, and no amount of reason or persuasion can dissipate them permanently. If the symptoms disappear as a result of this procedure, then suggestion should be given the credit.

It is possible that by painstaking reconditioning, symptoms may be changed, and the personality reeducated, but even with this method, suggestion plays a major rôle.

During the past few years there has been much discussion about treatment by psychoanalysis, and some therapists would lead us to the conclusion that psychoanalysis is the best, if not the only method of mental treatment, while other physicians who have but a smattering knowledge of the technic, condemn this method without reservation. Certainly it is not the only method of treatment. Every method has its advantages, and it is well to remember that not every patient lends himself to psychoanalysis; most physicians lack the special technical skill and training; and the method is so individualistic and time-consuming, that it cannot very effectively be employed in most cases. Perhaps the first criteria for the use of psychoanalysis is to gain insight into one's own character before trying to unravel the patient's problems. This may mean that the physician may need to undergo an analysis before attempting to analyze some one else. One thing is certain: most individuals cannot learn psychoanalysis from books and lectures alone. Above all, if the physician would do psychoanalysis he should have good sense, native understanding, and ethical conduct.

There are physicians who are apparently well trained in the technic of psychoanalysis, but they are slaves to theory, and the technic masters them, and they can see nothing beyond the horizon of sexuality.

As stated before, not all patients can be analyzed. The patient must be fairly intelligent, and sufficiently educated to understand the method and purpose of analysis. He must want to get well, and be prepared to perhaps change his whole outlook on life. In any case, it is expensive in time, energy, and money, for an analysis takes at least a year, and an hour daily may have to be spent for several months before any headway can be noted.

In a few words, the object of the physician in analyzing a patient is to direct the patient in the analysis of himself, and to thus make him aware of the significance of unconscious impulses. By such direction, he gains insight into the meaning of the symptoms which he wishes to be rid of. The physician does not even tell the patient what to do or say, nor does he lay down any rules, except possibly a few general ones. After all the unconscious material has bubbled over, and the patient's mind has literally undergone a catharsis, then the physician leads his patient into a synthesis and reintegration of his personality.

If the patient has been successfully analyzed, he is freed from unconscious conflict, and is capable of making an adjustment to difficult situations or at least meeting them in an objective way.

But not all analyses end in this theoretically ideal manner, because the character and personality may be too ingrained to permit of radical transformation. If a patient does not show definite progress for the better within six months or give promise of a cure within a year, the analysis should be discontinued, and certainly there is nothing to be gained by repeated analysis.

The psychoanalytic technic has been frequently changed within past years, and there is no indication that it has yet become stabilized. The

Freudian psychoanalysts are inclined to claim that no further supervision or guidance is necessary after the completion of an analysis, while the Jungian psychoanalysts state that the analysis is never completed and that there are no limits to personality development. It is obvious to every physician that no one ever attains such a degree of excellence that no further aid from others is necessary. A sickness may be ameliorated or cured, but there is no telling when there will be a "reinfection" or relapse. Although psychoanalysis has contributed more to our knowledge of personality forces than any other method of investigation, as a form of psychotherapy it is still in an experimental stage. Perhaps unknowingly, even before the announcements of Freud in 1895, physicians made practical application of the principles of psychoanalysis, and they undoubtedly will continue to do so as far as their experience and judgment permit.

Suggestion is the oldest and most widely used method of psychotherapy, and history is replete with examples of miraculous cures based on faith in some inanimate or animate object. It is impossible to eliminate suggestion from any form of treatment. Patients wish to be relieved of their suffering, and every physician knows that much of the medicinal and surgical treatment owes its beneficial effect to the element of suggestion. The tradition of medical and surgical procedures is so firmly established that even the most enlightened patient feels that something is lacking when treatment is carried out without "a laying on of hands."

Suggestion is associated with the subconscious mind, and as a great part of our life is subconscious, suggestion is at work in innumerable ways at almost every moment of the day. We are constantly receiving suggestions many of which may lie hidden and apparently lost in the subconscious mind and yet be hourly and daily shaping our characters. Perhaps these suggestions were first planted during childhood, for the human being is at no time more suggestible than during childhood. So indelibly are the impressions of childhood stamped upon the individual that they influence all the future life for good or evil to an extent that is astounding. Psychiatrists who have attempted to reëducate a warped or twisted character, are impressed constantly with the necessity for seeking the cause of the warp or twist in the half-forgotten experiences and memories of childhood.

Most people are slaves to their unconscious, the product of ancestral times and early habit patterns, and they constantly accept many facts without wonder and without any sensation of witnessing the miraculous, simply because these facts have become familiar. That shame or pleasure should cause a flow of blood to the cheeks, is so familiar a phenomenon that it causes no wonder. But if the memory of some unpleasant experience should cause an allergic-like skin reaction, the physician seems in a quandry. Every physician is familiar with the fact that worrying thoughts, or fright, have the power to upset the normal peristalsis of the stomach and intestines, but they may not realize that the secretions are altered, and indigestion, constipation, diarrhea, or colitis may be caused by the emotions.

Suggestions are constantly pouring in upon us from the sights we see, the sounds we hear, the people we associate with, the work we do, the books we read, the sermons or lectures we hear, the advertisements we observe, the radio announcements to which we listen, the plays, the movies, and the concerts to which we go. Suggestions are in fact influencing us the whole day long, and half the night. Some of them are accepted and acted upon, while others are resisted by counter-suggestion from higher authority. Many are apparently forgotten, but nevertheless are stored for all eternity in the subconscious mind, and perhaps continue to influence our lives momentarily. There is ample evidence to show that human beings are greatly influenced by the subconscious memories which in one way or other have been transmitted from centuries of ancestors. Humans fear the dark because of the subconscious memory of prehistoric days when the fall of night meant danger.

It is thus evident that not all suggestion comes from outside. The person may suggest ideas to himself. Some people live in constant apprehension, in constant expectation of developing some bodily ailment, and so are ready at any moment to interpret trifling symptoms as having a grave significance. Should they have slight indigestion and "heart burn," they are convinced by self-suggestion that they have heart disease, and promptly suffer palpitation and breathlessness. Fortunately in most cases such symptoms vanish with examination and assurance by the physician. In other cases, however, matters are made worse by the statement of the unscrupulous or ignorant physician.

If an article of diet once upsets the digestion, the patient is too apt, prompted by strong self-suggestion, to feel sick or be sick every time the article is served or even mentioned. There may be an allergy, but more often an unconscious fear. If the patient is raised to believe that fresh air is the mainstay of life, then he will suffer agonies, often quite disproportionate to the atmosphere of the room. Then there are the persons prepared to go on a voyage and to be sick according to the usual custom, and who become sick even if the vessel is unavoidably delayed. Or, the woman who has been told that nausea and vomiting are expected during pregnancy, so hyperemesis gravidarum develops. Perhaps a mother or grandmother suffered from dysmenorrhea, and the girl was told she could expect to be miserable when she menstruated for all women had the "curse," and so painful menstruation continued the tradition in the family. It was also a family trait to be constipated, to have sick headaches, or bilious attacks, and the newspapers and radio intensified the belief, and so the delusion was carried on from generation to generation.

But just as harmful suggestions may cause havoc in the human body, so helpful suggestions may bring good results. Fortunately hypnotism, which will be discussed later, though invaluable for some obstinate cases, is not the only way in which a helpful suggestion can affect the subconscious. Take, for example, happiness; sudden and unexpected happiness, under the

various forms in which it comes, is a most potent health-giving factor. When all medical remedies have failed to act, happiness has the power of making an immediate and convincing appeal to the subconscious self, and in the space of a few days the external signs of ill-health are gone, the eyes bright, the complexion clear, digestion normal, sleeplessness vanished, and health is restored as if by miracle.

As a rule, treatment by suggestion is given while the patient is awake, but in carefully selected cases, it may be best employed during sleep. When suggestions are thus given, the patient is put into a state of hypnosis. In this state, conscious resistance is reduced to a minimum, and the patient is put in a condition of heightened suggestibility. Since the conscious mind is in abeyance, suggestions are accepted without criticism by the subconscious mind and are put into action.

In an earlier paper,<sup>10</sup> I brought out the fact that it was unfortunate that hypnotism suffered the fate of other methods of therapy which have become associated with charlatanism and which have been hailed with undue enthusiasm. It fell into disrepute with physicians because, unlike psychoanalysis, it deals largely with symptoms rather than with causes. On the other hand, these arguments are hardly justified when it is realized that many standard methods of therapy are used by the charlatans, and physicians seldom know all the causes of an illness before attempting to treat it.

Hypnosis offers an approach to many psychogenic difficulties since it allows the physician to directly influence the subconscious. The dissociation brought about may serve as a gateway past resistances and allows indirect approaches to problems which otherwise could not be attacked. As is well known, one of the greatest obstacles in psychotherapy is to get the patient to consciously accept therapeutic suggestions. Under hypnosis it is possible to implant therapeutic ideas upon the "subconscious" and to have them take effect when endless numbers of suggestions given in the waking state would be given no heed or even actively resisted. Under hypnosis the patient accepts therapeutic suggestions, and acts upon them without conscious awareness and without building up defense reactions. Also, under hypnosis former dissociated experiences and amnesic material can be rendered available for re-association and reorganization. These statements sound overly enthusiastic, but it is not wished to imply that hypnosis offers a panacea. On the other hand, within limitations it is a valuable addition to the armamentarium of the properly trained physician.

The application of hypnosis requires no unusual personality or "strong will" on the part of the practitioner nor "weak will" or feeble intellect on the part of the patient. Any person willing to learn the psychological principles involved can perform hypnosis, but like psychoanalysis or any of the specialties, the practitioner should be duly qualified. It should be understood that the use of hypnosis is essentially a matter of technic, a technic of convincing and persuasive suggestion similar to that utilized every day in advertising and salesmanship. Just as almost anyone may be a hypnotist,

so practically anyone may be a subject. The best subjects are highly intelligent patients with good powers of concentration. There apparently is no difference between the sexes, although the younger adults or adolescents are more receptive, and extroverts are more responsive than introverts.

Like any form of psychotherapy, the results of hypnosis are individually limited, and vary in degree and variety with every subject, depending, of course, upon the innate endowment of the patient. Furthermore, all phenomena do not necessarily occur in every subject, but only manifest themselves as a rule. Some patients fail to show this or that particular characteristic response to hypnosis.

The mechanism of normal sleep and that of hypnosis are the same. Normal sleep, like hypnosis, is a condition of dissociation. In fact, spontaneous somnambulism produced in normal sleep can be transformed into hypnosis, and this in its turn can be terminated in normal awakening or normal sleep. The physician can not infrequently influence by suggestion a normally sleeping person and transport him into hypnosis without awakening him. It is still easier, in the reverse direction, to transform hypnosis into ordinary sleep by suggestion.

Physiologists have done a great deal of work with sleep in an attempt to explain its mechanism. There is no doubt that through the process of association the vasomotor reflex centers can be stimulated. Also the reflex centers for the closure of the orbicularis oculi muscle may be stimulated, and thus call forth the neurodynamic processes which bring about sleep. This mechanism may also be brought about by exhaustion or drug action on the cortex. Stimulation of the vasomotor centers brings about an increasing anemia of the brain, with its accompanying dullness, and sleep. When this condition progresses sufficiently then the person loses touch with reality and dissociation takes place. Dissociation is when the normal constellations are deflected from their usual distribution and activity.

Hypnotic suggestion is a method of invading the associated dynamics of the brain. It may be used to dissociate that which was associated, or to associate that which was not associated before. From what has been said before it is evident that at first its chief invasion is an inhibitory one, as it dissociates the associated automatisms of the brain. The dissociated dynamics of the brain of the person under hypnosis are in a condition of receptivity or hypotaxis, as compared with the well-concentrated and associated dynamics of the physician, which press suggestions upon the patient's subconscious by way of the special sense organs. The patient becomes plastically moldable, and is compelled to adapt himself more or less irresistibly to the physician's suggestions. The cause of this apparent subordination does not lie so much in the strength of the physician as in the patient's feeling and conviction that he is being subjected to a dynamic influence. All persons are in a condition of hypotaxis, or dissociation during normal sleep, and confuse dream thoughts with actual occurrences. It is for this reason that sleep is advantageous for the application of suggestion.



During sleep even the most "powerful" brain or well integrated personality obeys the suggestion of an otherwise less "powerful" brain, which is awake and in an associated condition.

The physician who wishes to use hypnosis must know how to convince his patients that he is capable of doing so, and he must be able to more or less induce an enthusiasm for this form of treatment. Thus the practitioner must either be convinced himself, or, failing this, possess a dramatic personality, in order to convince others. Everything which fills a person with enthusiasm gains control over his brain activity, easily conquers all the contrary impressions, and leads the person into receptivity. Therefore, the hypnotizability of a person increases with his enthusiasm and with his confidence, as well as with the enthusiasm and former success of the practitioner. And, vice versa, it sinks with the abatement of the enthusiasm, with mistrust, and with failures. On the other hand, many other individual factors as mentioned before also assist in the application of hypnosis, such as individual plasticity and intensity of the impressionability, exhaustion, sleep capability, etc.

As the patient goes into hypnotic sleep, the field of consciousness narrows and external stimuli, except those given by the practitioner, lose their significance. Ultimately the subject loses contact with the external world except for the operator. Essentially, the "conscious" loses control, while the "subconscious" is left in rapport with the physician. This rapport, which is one of the important phenomena of hypnosis, may be defined as a state of harmony between the patient and the physician, with a dependence of the former upon the latter for motivating and guiding stimuli, and is similar to the "transference" of the psychoanalytic situation. It enables the practitioner to remain in full contact with his patient while to the rest of the world the hypnotized person remains unresponsive. Nevertheless, under hypnosis this rapport may be transferred by the command of the physician to any designated person.

As has been brought out, hypnosis comes as a result of coöperation. Without full coöperation between the patient and the practitioner there can be no hypnosis. Unwillingness to be hypnotized, admitted or concealed, prevents this essential coöperation and consequently hypnotic sleep does not and cannot occur.

As long as the aforementioned essential principles are observed, the exact technic of inducing hypnosis is of secondary importance, but the physician should vary the details of his technic to fit the individual patient, and it is unwise for the physician to say that he will or can hypnotize anyone until he has made a trial. The fact that a previous hypnotist was unsuccessful is not necessarily proof that he will fail. Success is not precluded by the patient being restless or showing uncontrolled movements. The patient's consent should first be obtained and, in some cases, this should be in writing. The physician should disregard a statement such as "I had such a good night that I do not feel sleepy." Often on the first occasion

an audience may distract the patient as well as the physician but it is hazardous to be alone with a woman, so a witness should be present. Before starting the hypnosis, the practitioner should write down the items he wishes to find out or suggest, and write down also the results directly they occur, as it may be impossible to remember the phase to which each of them belongs. If he plans to suggest disappearance of sensory anomalies he should first know accurately the patient's reactions to stimuli.

The first attempt to induce hypnosis may produce either a slow or a rapid sleep, but afterwards sleep as a rule is rapid. Occasionally after a rapid induction the patient resists sleep subsequently and the second induction is slow. Although the patient's coöperation, as well as his consent, is necessary at the outset, once the patient has been hypnotized the physician will thereafter succeed in placing the patient under hypnotic control if proper technic is followed.

In most cases the patient should be asked to sit in an easy chair or lie down, and relax his muscles. Many people find it difficult to relax, even though their attention has been immobilized. He should not be told to think of nothing at all, for this is impossible. It is well to ask him to imagine himself somewhere where the scene is familiar, pleasant, and neutral, such as a park or in bed at home, and pretend to feel drowsy. He may be able to help this simulation by emphasizing his expirations. He should pay no attention to the physician at the beginning of the procedure; for illustration, the ease of attention in church can be advised. The patient is then told that he will be instructed when he is to start listening, for this is not required until after dissociation has occurred. The patient is then told to look at the physician and at once is told to transfer his gaze to some object which is held in front of his eyes, such as the index finger and thumb, a pencil, or an examining light. He is told to continue to stare at it, if possible without blinking. As a rule a bright object is best, but the object is immaterial. During this stage the physician should suggest ocular fatigue, speaking in a monotone but confidently. It is seldom necessary to make any passes and many patients dislike it, although it may be useful in obtaining relaxation. The physician should bring the object nearer and nearer to the patient's eyes and tell him that he can no longer keep them open. When the lids have closed he is told that he is unable to open them of his own accord. If dissociation takes place the faculties are at once reduced but they can be restored to full activity at a word, without waking the patient. There are several features in this technic which resemble those of putting a child to natural sleep.

In general, staring into the patient's eyes is inadvisable, as the effect produced by eye on eye is considerable and may be unpleasant. It may impress the patient too much, although in selected cases this may be desirable.

At the moment of dissociation the eyes rotate upwards and the expression alters. The patient may become restless for a few moments. Rota-

tion occurs the instant before the lids close, and cannot be voluntarily controlled. Sometimes a patient will appear to make a great effort to remain associated, opening his eyes at once and relaxing his rotation; he may repeat this behavior several times. A few words by the physician makes dissociation complete. Rotation takes place in the natural movements of blinking and also in natural sleep, although it is absent in general anesthesia. It does not always persist during sleep. In blinking it occurs simultaneously with the dropping of the lids and is thus unobserved. The individual himself is unaware of it.

If after the hypnosis the lids are opened the rotated eyes are seen not to be squinting, as is the case in natural sleep. The pupils usually come down and are directed forwards as the lids are separated, and then they may wander laterally, with squint.

Where there is some difficulty in getting the patient to relax, he may be given a hypnotic drug to assist in the induction of controlled hypnosis. The barbital compounds, bromides and paraldehyde may be used, but the essential principles as above outlined also have to be followed. If these drugs are used, they should only be used for the initial inductions, as in many cases the results are unsatisfactory because the chemical effects frequently interfere with manifestations of the hypnotic phenomena. It is well to remember that drugs should not be used in ambulatory patients, as the patient should be allowed to sleep off the chemical effect of the drug before awakening, otherwise the "hang-over" will act as an auto-suggestion. Also, the routine of awakening the patient by suggestion cannot usually be followed if drugs are used to induce hypnosis.

When undergoing hypnosis the patient first begins to be drowsy and to feel sleepy; and, if he wishes, he can at this stage stop the hypnosis. This stage is known as somnolence, and it is during this stage that external stimuli are most liable to distract the patient's attention. His confidence may thus give way and he awakes himself, and refuses to follow further suggestions. In spite of the fact he can resist suggestions, he can only do so with a certain amount of difficulty.

As the patient goes deeper into hypnosis he concentrates more and more on what the physician is saying to him, external stimuli have less and less effect, and the patient finds himself doing automatically what he is told to do. In this stage, known as hypotaxis, the patient's eyes are closed and he cannot open them except on the express order of the physician. In fact nothing can be done except it is ordered, and then it must be done. The patient may describe his feelings as if his mind were separated from his body, and as if he were able to watch his body behave as though it had nothing to do with him. He may recall this dissociated experience as if he were recalling a dream.

If the patient goes into deepest hypnosis, known as somnambulism, he has given himself up completely to the physician. He will walk about and perform all kinds of actions, and there will be complete amnesia, if the

practitioner orders him to forget or if the patient himself believes he will not remember what has happened. On the other hand, many patients are apprehensive about this point, and they must be reassured that they will remember everything that happens while they are under hypnosis, if they so wish. However deep the hypnosis, the patient will remember everything if he is told to do so.

Most patients can be put deeply under hypnosis at the first session, although some may require three or four sittings before the deeper stages of hypnosis are reached. The patient needs to be reassured that because he did not go deeply under the first time is no reason that he can not be hypnotized.

Once a patient has been successfully induced into hypnosis he can be conditioned to become dissociated instantly and apparently deeply on future occasions, in response to any signal which has been selected. This may be a stare, a click of the fingers, a written word or a word spoken in a whisper. It is immaterial whether the patient is alone or in a crowd, but he must understand the significance of the signal. He can also be conditioned to hypnosis by radio or telephone. Reassociation in response to a signal occurs equally rapidly and, once again, dissociation. Both phases can be produced without any coincident eye change or alteration of the features so that it may be impossible for an observer, even with the closest scrutiny, to identify the patient's condition.

If the physician wishes the patient to reënter his influence by spoken word, sign, letter, telephone, telegraph, or radio, he can usually ensure it even at a distance, by giving instructions either before, during, or after hypnosis. If reëntry is not desired he should counter order it before he wakes the patient. If this preventative is not administered, any of the three stages of hypnosis may occur spontaneously and may be mistaken for absentmindedness, spontaneous trance, the loss of identity as in hysteroid epilepsy, or something more serious.

As brought out in my former paper <sup>16</sup> it is within the realm of possibility that some of the compulsion neuroses and the hallucinations of the psychoses may be explained by this same mental miscarriage. It has been shown that thought processes passing through the brain can be detected and even measured by electric oscillations. Also the temperature of the body can be raised and vasomotor changes effected by passing radio currents through the body. It is not far-fetched to assume that sensitized persons suffering from certain atomic changes in their tissues may thus tune their special senses or brain cells into a specific radio frequency and so become sensitive to suggestions that are known to be always passing through the ether, and which are normally detected by means of radio receivers or will be detected when proper instruments are devised. These "sick" persons are in various degrees of dissociation and hypersuggestibility and so may misinterpret these stimuli. On the other hand, these "radio" suggestions planted in the brain of the patient may set up auto-

suggestion and so lead to compulsions, just as suggestions given to a patient under hypnosis may direct his actions after he awakens.

A patient may pretend to be hypnotized or may deny afterwards that he was under hypnosis. After hypnosis there is no yawning, and no laughter, although the patient will laugh if he is told to behave naturally. When he is told to walk about and do things his eyes are as a rule directed forwards and the lids almost closed. He opens his eyes directly he is told. Some patients maintain the upward rotation as they walk about and, being unable to see where they are going, bump against furniture; it is notable, however, that they do not grope their way as a blind man does and as a man might if he were pretending to be hypnotized. The persistence of rotation and eye closing may be due to the physician's insistence on "You cannot open your eyes," during the induction. Rotation sometimes persists with the lids open, but ceases when the patient is told to look forwards. Flickering of the lids, due to restless eyes, indicates that the patient is not under hypnosis. It might be expected that the patient at the moment of dissociation would drop something which had been put into his hands, but he does not let go unless he is told to do so. The physician's influence over the patient's conduct has no special value for differential diagnosis for, if the patient is pretending he will do most unexpected things if he is told. A note should be made of what is said to him and his replies, so that he may be tested later. If he has been under deep hypnosis, and has not been instructed to remember what he was told while asleep, he will recall nothing, but if he has been pretending he may repeat the conversation out of ignorance.

The physician may believe that the patient is hypnotized whereas he has merely fallen asleep. Although a patient may become hypnotized during the procedure it does not follow that he is under the physician's influence; it may be found that he does not talk to the physician and that the physician cannot rouse him. This condition may be due to his reentry into the influence of a previous hypnotist, a state which the procedure has suggested.

The failure of suggestions to be followed is no evidence that hypnosis has failed. In seeking to demonstrate the influence on a patient's muscular power it is well to remember that he may show very great power by an effort of will, although it is in hypnosis that the extremes of flaccidity will be manifested. As regards the sensory side, a patient awake may bear a great deal of pain without showing it, if he is so minded, and every physician has seen profound alterations in sensibility, involving even the cornea.

There is no reliable criterion of depth of hypnosis, but perhaps the distance of memory recall and the subject's readiness, after being awakened, spontaneously to reenter the physician's influence may be so regarded. A patient has no better knowledge of the duration of his hypnotic sleep than he has of normal sleep. Failure to obey is apparently no criterion of the depth of hypnosis, nor is difficulty in waking the patient; but the physician should have no difficulty along this line, provided the patient slept for him

and remained under his influence. Whatever the apparent depth of the hypnosis, a patient may wake spontaneously even in the face of a continued order not to do so, and this is particularly liable to occur if the eyes are investigated or if a suggestion is unconvincing or unacceptable.

On waking, the patient may rub his eyes and seem dazed, but he does not yawn. If he complains of headache it is slight and transient. Some patients appear to have no knowledge whether sleep has been artificial or natural.

If during the hypnosis the physician had arranged for a substitute to wake the patient he can leave the patient without feeling anxiety, but if this has not been done the patient will either remain under hypnosis until he awakens spontaneously, or he will transfer himself into natural sleep from which he will awaken in due course or from which he can be aroused by anyone. It is well to remember that a general anesthetic may cause the dissociation to give way, or the physician can give a demand to awake over the telephone and thus awaken the patient.

Failure to put a person under hypnosis is fairly common even though success can ultimately be attained, and the reason lies with the patient rather than the practitioner. He may be over-interested or distracted; a tight garment or a distended bladder is enough to prevent hypnosis at the first trial. The patient may fall asleep or may sleep naturally after first passing through a brief stage of hypnotic sleep. There may be coöperation and yet sleep may have been forbidden by a previous hypnotist, either when the patient was awake or under hypnosis. The patient may protest that he is coöperating, whereas he is strongly resisting, and this may be due to an anxiety about the procedure in general or to a fear of what he may be caused to do or say as a result of hypnotic suggestion.

If the patient is a receptive individual, and the physician has been careful to properly apply the technic, there is no telling what symptoms can be removed by hypnotic suggestion. Care of course should be taken not to suggest a movement of an arm or leg that is organically paralyzed, or to try to bring back the memory of an amnesia victim in whom there is extensive brain destruction. But, the experienced individual is often surprised by the dramatic results that unexpectedly occur in cases that he may consider beyond help. A long standing paralysis that has resisted all other forms of treatment, may immediately recover under hypnosis. A case of amnesia may be awakened into reality. An insomnia case may sleep like a baby. And even in cases of obvious organic pain, such as childbirth, amputation or laparotomy, the patient may go through the ordeal without flinching, and in any case show better response to the anesthetic, if hypnotic suggestion is used.

#### SUMMARY AND CONCLUSIONS

1. Psychotherapy begins the moment the patient enters the physician's office, and the patient's confidence should be established by a careful medical and social history, followed by a thorough physical examination.

2. Placebos are justified, but their effectiveness is in direct proportion to the amount of suggestion they embody.

3. Psychoanalysis may be successful in selected cases.

4. Suggestion is continually affecting the subconscious mind, and may influence the person for good or bad.

5. Hypnosis has a definite place in psychotherapy, as it is not a mysterious art, but a scientific technic.

6. Under hypnosis the patient has increased suggestibility, and any suggestion not objectionable to the subject will be accepted and acted upon. Thus hypnosis may be used to overcome many functional symptoms, and to supplement other forms of psychotherapy.

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# THE PROBLEM OF RHEUMATISM AND ARTHRITIS

## REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1937

(Fifth Rheumatism Review) \*

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##### Part II

#### HYPERTROPHIC (SENESCENT, DEGENERATIVE, OSTEO-) ARTHRITIS

It has been reliably reported that practically every person aged 50 years or more can be shown to have hypertrophic arthritis but that only about 5 per cent have symptoms of it. At that rate, in 1935 there were at least 23,726,900 Americans with hypertrophic arthritis, of whom presumably about 1,200,000 had symptoms. But in spite of its great incidence this

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disease remains a neglected stepchild in the family of rheumatism. Although hundreds of reports on rheumatic fever, on gonorrheal arthritis and on atrophic arthritis appear annually, few appear in which hypertrophic arthritis is the sole or chief topic; less than six appeared during the year reviewed. Certainly a disease so prevalent and distressing, even if not as tragic as atrophic arthritis, deserves more serious consideration than to be used almost exclusively as a source of control material by those studying the chemical, immunologic or roentgenologic reactions in atrophic arthritis. A comparison of three current reports (Buckley; O'Reilly; Ray) fully discloses the incompleteness of knowledge of the disease, not only of its etiology but even of its clinical and roentgenologic picture. For example, most writers regard Heberden's nodes as the commonest expression of hypertrophic arthritis; one writer,<sup>511</sup> however, stated that Heberden's nodes practically never occur in (what he calls) osteo-arthritis and that their pathologic characteristics have nothing in common with those of osteo-arthritis. According to one physician<sup>563</sup> in osteo-arthritis terminal and also carpometacarpal or metacarpophalangeal joints may be affected; according to another,<sup>84</sup> terminal phalangeal joints are affected before proximal (interphalangeal) joints but the wrists and metacarpophalangeal joints "invariably escape"; according to a third writer,<sup>511</sup> hands are never affected in "osteo-arthritis." According to Buckley, spinal osteophytes are manifestations of osteo-arthritis; according to O'Reilly, simple osteophytic liping does not, per se, constitute osteo-arthritis.

*Definition.* With such ideas in conflict, obviously there is as yet no final agreement as to the proper clinical and roentgenologic definitions of hypertrophic (osteo-) arthritis. Writers are finding it increasingly necessary to qualify the terms "hypertrophic" arthritis and "osteo-arthritis." We have discussed in previous Reviews the importance of realizing that the clinical picture and the roentgenologic picture of hypertrophic arthritis are not necessarily synonymous and that a roentgenologic pattern of bone hypertrophy (hypertrophic arthritis in the roentgenographic sense) is a feature which may be present at certain phases and in certain joints (weight-bearing ones especially) in many types of arthritis which are clinically entirely different (traumatic, gonorrheal, gouty, psoriatic, even atrophic arthritis). Therefore hypertrophic arthritis, roentgenologically speaking, is by no means always the equivalent of hypertrophic arthritis, clinically speaking. To make these distinctions more clear some believe that the clinical syndrome should be named, "primary hypertrophic (or osteo-) arthritis" to distinguish it from the several roentgenographic patterns of "secondary hypertrophic arthritis" seen during the course of a number of articular diseases.

[One of us, P. S. H., frequently has found it clarifying to combine etiologic (?) and roentgenographic terms, and to speak of "senescent hypertrophic arthritis" as distinguished from "gouty hypertrophic arthritis" or "traumatic hypertrophic arthritis," and so on. But it must be realized that, as the disease progresses roentgeno-

graphically, what is senescent hypertrophic arthritis or gouty hypertrophic arthritis one year may, as time passes, be more correctly described later as "senescent destructive arthritis" or "gouty destructive arthritis."—Ed.]

In line with this conception, Race and Ray noted that "secondary osteo-arthritis" may be the sequelae of rheumatoid arthritis in weight-bearing joints, of gout and of certain diseases in which marked decalcification occurs, such as osteitis deformans. O'Reilly defined his conception of (primary) osteo-arthritis, which will be discussed later, and noted that in certain joints never affected by primary osteo-arthritis, osteo-arthritic changes (i.e., secondary osteo-arthritis) occasionally occur secondary to known causes (fracture, chronic trauma, rheumatoid arthritis, and so on) but "they are not osteoarthritis." Thus, the simple lipping such as one often sees in a bunion joint of the great toe is not true osteo-arthritis, according to O'Reilly, but a physiologic response to constant trauma.

[Would it not have been clearer had he stated it thus: The lipping often seen in the great toe is not evidence of senescent (or primary) hypertrophic arthritis but of a physiologic response to trauma; i.e., traumatic hypertrophic arthritis (or, to use the English synonym, secondary traumatic osteo-arthritis)?—Ed.]

*Incidence.* Of 9833 patients admitted in three years to the Devonshire Hospital, Buxton, 1069 (11 per cent) were classified by O'Reilly as having true osteo-arthritis. Because the disease begins and may progress insidiously before producing symptoms, statistics on age incidence refer to the onset, not of the disease but of symptoms. Among 94 patients, O'Reilly noted the following age incidence: four cases (4 per cent) between 30 and 40 years; 21 (22 per cent), between 40 and 50 years; 42 (46 per cent), between 50 and 60 years; 22 (23 per cent), between 60 and 70 years, and five (5 per cent), between 70 and 80 years. As Miller noted, one occasionally sees typical hypertrophic arthritis, with Heberden's nodes, affecting patients considerably less than 40 years of age.

Ray noted the usual predilection of the disease for weight-bearing joints and for those used in certain occupations but O'Reilly noted no special occupational incidence in 100 cases.

*Clinical Data.* The orthodox clinical picture was again described.<sup>84, 473, 563</sup> Miller noted that prodromal symptoms of hypertrophic arthritis are not so numerous or so striking as those of atrophic arthritis but "may include headache, malaise, impaired digestion, sluggishness of bowels and a disturbance of metabolism."

[We are not inclined to agree with this statement. These symptoms are common to persons of this age group whether they complain of hypertrophic arthritis or not; we have not noted these prodromes with sufficient frequency or consistency to consider them to be related to the disease.—Ed.]

O'Reilly and Buckley emphasized an insufficiently recognized point: Hypertrophic arthritis is generally associated with considerable "senescent fibrositis" or "fibrositis of the degenerative type." Subcutaneous nodules

are rarely or never seen in hypertrophic arthritis, according to Miller. Already noted were differences of opinion as to the "articular geography" of true hypertrophic arthritis. According to Ray, the thumb base is commonly affected and either carpometacarpal or metacarpophalangeal articulations may be affected. According to Buckley, terminal finger joints are affected before interphalangeal joints, but metacarpophalangeal and wrist joints "invariably escape" in true or primary osteo-arthritis.

[From the micropathologic standpoint, practically every joint of persons more than 50 or 60 years of age is affected with at least the first stages of hypertrophic arthritis, i.e., with degenerative fibrillation of cartilage, precursor of later hypertrophic bone reactions. Roentgenographically also, certain joints of persons more than 50 years old (e.g., those of the spine) are almost always affected. But although most of his joints might be shown microscopically to be affected with degenerative changes (precursors of hypertrophic arthritis) the elderly patient generally will note symptoms only in certain joints and practically "never" in others. Thus, the disease clinically affects knees, cervical and lumbar spine and terminal phalangeal joints commonly; sacro-iliacs, interphalangeal joints and hip less commonly; metacarpophalangeal joints and wrists rarely if ever.—Ed.]

In spite of their great frequency there is strangely no common agreement as to the anatomic nature of Heberden's nodes. Heberden's own description was so meager that it has permitted to arise many diverse clinical, pathologic and roentgenologic definitions. Current papers reveal this confusion. According to Buckley, degenerative fibrositis "may appear as Heberden's nodes which gradually become ossified and constitute one form of osteo-arthritis differing from other forms in that (still according to Buckley) the articular cartilage is unaffected. These nodes appear at the bases of the terminal phalanges and are at the beginning cystic in character, filled with a gelatinous substance." Ray's interpretation follows: osteophytic outgrowths often affect terminal phalangeal joints but "osteophytic outgrowths are not quite the same as Heberden's nodes which spring from epiphyseal ends of the bone. One would say that an osteophytic outgrowth that was causing distortion was not a Heberden's node because the latter do not give rise to any displacement of joint surfaces." According to O'Reilly, Heberden's nodes are not a part of, and rarely occur in, "osteo-arthritis" (only once in 50 consecutive cases): "their pathology has nothing in common with osteoarthritis."

[In our opinion Heberden's nodes merely represent the nodular, bony processes at the terminal phalangeal joints which are but a part of the soft tissue, cartilage and bone reaction of primary hypertrophic arthritis at those joints; in the late stages of this process cartilaginous destruction and lateral displacement of the joint may occur.—Ed.]

Overweight affected only 12 per cent of O'Reilly's patients. In hypertrophic arthritis, pain results from capsular changes, according to O'Reilly; only those motions which stretch the capsule produce pain. Synovial changes and capsular fibrosis account for the stiffness; muscle wasting,

"some of which is constant," produces the weakness. Other features considered characteristic by O'Reilly will be noted later.

*Roentgenograms.* The usual changes were reviewed.<sup>84, 235, 511, 563, 604</sup> Using an "improved technic," roentgenograms of flexed knees, Jordan<sup>352</sup> and Holmblad obtained better views of intercondyloid fossae, thereby noting early osteo-arthritic changes not visible in ordinary roentgenograms.

*Pathology.* The pathologic reactions were reviewed.<sup>511</sup>

*Laboratory Data.* Blood counts in a few cases were normal.<sup>511</sup> Arneth counts were generally normal; occasionally abnormal in either direction.<sup>372</sup> Sedimentation rates were normal in 100 per cent of 25 cases,<sup>28</sup> and in 83 per cent of 53 cases<sup>511</sup>; they were normal in only 59 per cent of Lautman's 82 cases. Saline absorption tests gave negative results.<sup>372</sup> Glucose tolerance tests gave negative results in 13, slightly positive results in three of 16 cases.<sup>372</sup> Among 26 cases, blood creatine was increased in none; creatinine in 31 per cent. Urine contained creatine in 8 per cent; increased creatinine in 8 per cent (Moreno). Hepatic dysfunction, as determined by the rate of excretion of azorubin S, was present in four of 15 cases (Rawls, Weiss and Collins).

*Etiology and Pathogenesis.* Ray accepted hereditary "articular inferiority" as one of the chief causal factors. The cartilaginous changes due to normal wear and tear were called "attrition lesions"; their exaggeration by chronic trauma (from knock knees, loose bodies, obesity, lax ligaments and muscles) leads to hypertrophic arthritis (Collins). Such changes resulted in knees of rabbits when Bennett and Bauer experimentally produced chronic (four to 28 weeks) patellar displacement; degenerative and hypertrophic changes in cartilage, eburnation of subchondral bone, connective tissue proliferation and marginal overgrowth at the perichondrial margins of articulating surfaces developed. Similar reactions were noted in a case of chronic bilateral patellar displacement.

Little or no support was found for the theory that local or general degenerative vascular changes cause the disease. Among 56 cases, O'Reilly found elevated blood pressures in 36 per cent; myocardial degeneration in 16 per cent; thickening and tortuosity over superficial arteries in 16 per cent; incidences normal for the age group. Furthermore, examination of the small vessels in joint tissues disclosed no signs of disease. According to Kling, interference with articular blood supply from juxta-articular adiposis dolorosa may be one of the causes of hypertrophic arthritis. Painful fatty masses were present in 10 to 15 per cent of his cases of hypertrophic arthritis. Each of 112 patients with juxta-articular adiposis dolorosa complained of pain and disability in contiguous joints and, in a large number, osteo-arthritic changes of varying degrees developed (articular spurring in 57 per cent). The fatty masses presumably interfere with articular circulation by diverting blood from the deep articular tissues (capsule and periosteum) and also by obstructing (through pressure) the blood flow in deep veins, favoring varicosities therein. Kersley found no char-

acteristic changes in nail-bed capillaries. No definite evidences of *endocrine disturbances* were noted.<sup>511</sup>

Factor of infection; bacterial; mycotic. It was generally agreed that bacterial infection seemed to play no rôle but O'Reilly gave a novel slant to the infectious theory. He expressed the belief that osteo-arthritis is a degeneration of joint tissues consequent on chronic inflammatory changes in the lymphatic connections of the joint and due to mycotic infection of the skin of the feet.

O'Reilly's argument follows: The only joints affected in (true) "osteoarthritis" are hips, knees, and lower spine. For reasons which were rather cursorily given, he stated that all the hypertrophic bone changes occasionally seen in other joints are "osteoarthritic changes" secondary to known causes such as gross trauma or fracture; "these osteoarthritic changes are not osteoarthritis," nor are they a part of the disease. Heberden's nodes were excluded as having nothing in common with osteoarthritis. In 50 cases, joints affected were lower spine in 48, left knee in 45, right knee in 41, left hip in 36, right hip in 31 cases; in 21 cases all five regions were affected. "A disease whose incidence in the body is so constant must have an anatomical path of spread. The lymphatic connections of joints provide this path." In 68 per cent of his cases he noted in roentgenograms, small, discrete, calcified lesions in the pelvis, found at necropsy to be calcified tissue in lymph nodes along pelvic vessels. Microscopically, the iliac (but not the popliteal or epitrochlear) nodes gave evidence of chronic inflammation with fibrosis and occasional focal calcification in the fibrotic lesions. O'Reilly sought an explanation of the adenitis. In all cases he found in the feet erosions, whitish patches of sodden skin, not infrequently fissured, in the fourth interdigital space, generally also infections of toe-nails (yellow tinge, loss of translucence, brittleness going on in neglected cases to onychogryphosis). On cultures of affected skin and nails in 20 cases monilia grew in 19; epidermophyton in one. The foot infection was considered responsible for the inguinal adenitis which in turn was the cause of the iliac adenitis (iliac nodes receive lymph from inguinal nodes). Joints and the lymphatic system are closely connected, as synovial membrane is richly supplied with lymphatic vessels. "The iliac glands form a theoretical focal point from which a disease process spreading along the lymphatics would involve the joints which are actively involved in osteo-arthritis" (knees, spine, hips). Joints of the feet and ankles are not involved because they are connected, not with infected inguinal or iliac nodes, but with noninfected popliteal nodes.

[This explanation seems very hypothetical. We do not consider it proved that primary hypertrophic arthritis affects only the joints stated. It is necessary for O'Reilly to make this assumption; otherwise his anatomic explanation would be more difficult to prove. Isn't the skin of the toes connected with the same lymphatic structures as the joints of the toes? If so, in the presence of a foot infection, why aren't the popliteal nodes, which drain the joints of the feet and ankles, infected and why aren't the toe joints not less, but more, likely to be involved? The idea seems unproved.—Ed.]

*Treatment.* Although little can be done to correct the senescent changes which are the basis of hypertrophic arthritis, by improving working conditions much can be done to lessen the factor of occupational or other chronic trauma which accelerates the senescent lesions (Buckley; Race). Buckley regarded no treatment as of the slightest use for osteophytic outgrowths or Heberden's nodes. Diets, with restrictions of carbohydrates, seemed value-

less (Cmunt) except as they help to remove trauma of obesity (Buckley). Removal of foci was approved only for local reasons, or as a matter of general hygiene (Hamilton; Snyder). Those who have prescribed sulfur or concentrated vitamin D have made little or no distinction between atrophic and hypertrophic arthritis, claiming results in both types indiscriminately. Farley and Steck considered massive doses of vitamin D very helpful. Sulfur was advocated by Clark, Wheeldon, Woldenberg, and Parmenter; of Parmenter's 22 patients so treated, 81 per cent were variously improved, the rest were not relieved. Gold therapy was considered by Hartfall, Garland and Goldie relatively unimportant for hypertrophic arthritis: of 68 patients treated, none were cured; improvement was marked in 10 cases, moderate in 11, slight in 19, absent in 22; six patients became worse.

"There seems little scientific basis for" the continued use of vaccines in hypertrophic arthritis (Jordan).<sup>351</sup> Injections of chaulmoogra oil provided only slight temporary analgesia (Robinson).

Literature on roentgenotherapy for hypertrophic arthritis was briefly reviewed by Fineman and by Kahlmeter. Various opinions on its value have been expressed, in the main favorable (Hernaman-Johnson). Kahlmeter considered its effects purely analgesic. Pains in osteo-arthritic hips seemed to him to arise not so much from intra-articular changes as from painful hyperfunctioning muscles of hip, thigh and back. Roentgen-rays may have some direct influence on these painful muscles. Of 10 cases in which *fever therapy* was given by Simmons, late results were: no relief in five; marked improvement in one; moderate relief in two; slight relief in two. Bierman's results were "poor" (no details). Iontophoresis with *mecholyl* (acetyl-beta-methyl choline) seemed of value to some: of 47 patients of Martin and Eaton, 26 per cent became "well"; 53 per cent were improved; 24 per cent not improved. Six of nine patients of Boyd, Osborne and Markson noted decreased pain and increased motion; three were unimproved. Kling and Sashin preferred *histamine* iontophoresis: of 51 patients, 33 (65 per cent) were "cured or improved"; the rest were not. Among Young's 10 patients treated with histamine ointment, improvement was marked in five; absent or slight in the rest. The oral use of thyroid or iodides was recommended by some (Kersley; Ray). To O'Reilly the early treatment of monilia infections of feet seemed most important.

Physical therapy. The various forms of physical therapy used for atrophic arthritis were advocated for hypertrophic arthritis also. Immersion of hands, covered by rubber gloves, in hot water 20 minutes daily was recommended.<sup>563</sup> The effect of short wave therapy was only that of heat.<sup>355</sup> For painful hips caliper splints properly applied may relieve pain but often are considered more uncomfortable than the pain.<sup>354, 563</sup> New braces for knees<sup>352</sup> and for hips<sup>376</sup> were described. To relieve pain in affected basal thumb joints Ray advised molded leather wrist casings.

Surgical procedures. These occasionally may be indicated for painful hips. Henderson evaluated the various orthopedic measures and considered

manipulation under anesthesia, celiotomy and remodelling of a femoral head, each useful for maintaining or increasing motion in selected cases. Arthrodesis is rarely acceptable to patients. Judgment was reserved regarding acetabuloplasty. A "new" procedure, bone puncture or forage (used by Nobel Smith 1890; by Mackenzie 1931, 1932, 1936; by Graber-Duvernay 1932, 1933, 1935) was employed by Henderson and Simpson in 12 cases of painful hypertrophic arthritis of hips: seven noted "definite lasting relief" from pain; two received temporary relief but pain gradually returned within six months; three noted no relief. Relief of pain was noted during the first postoperative week in five cases (but was lost in one case), three months after operation in one and seven months after operation in another. [This raises the question as to the relation of the relief to the operation.—Ed.] Bone drilling of femoral epiphyses seemed of value only in cases in which the arthritis was advanced. The procedure was relatively simple. Patients stayed in the hospital an average of only 10 days and were usually out of bed, walking, seven or eight days after operation.

#### BACKACHE AND SCIATICA

*General Remarks.* In the past it has often been so difficult to find the exact cause of any given back pain, and patients have been so unsatisfactory to treat that they have been accepted with distaste and pessimism by most physicians; a backache was just another "headache" to the physician. The problem is still a complex one and as Galland wrote, "a discussion of low back pain should be entered upon with a spirit of humility, for this is a topic upon which no physician in the present state of knowledge has the right to be dogmatic." Because of recent advances in knowledge of the pathologic physiology of the back the interest of physicians therein has greatly increased and papers on the subject have increased accordingly. It is impossible to review them adequately here, filled as they are with a mass of clinical and statistical details concerning the inter-related anatomic, roentgenologic, neurologic and pathologic aspects involved.

*Causes of Backache and Sciatica.* Major causes of backache were listed<sup>616</sup> as (1) neurologic, (2) gynecologic, (3) genito-urinary, (4) orthostatic (postural and from developmental anomalies) and (5) osteo-arthritic. Detailed working classifications<sup>253, 254, 458</sup> were given (table 2). Causes of backache and sciatica, particularly low back pain, are so numerous that a proper study involves careful local and general physical examinations, frequently special examinations (neurologic, urologic, gynecologic), roentgenograms often made at various angles (anteroposterior, lateral, oblique, stereoscopic), often examination of spinal fluid and spinal roentgenograms with injections of lipiodol. The technic and significance of the various tests and physical maneuvers for localizing and differentiating lesions affecting the lower back were again discussed.<sup>23, 254, 256, 451, 470, 501</sup> Roentgenologic methods for studying spines and the special points to be noted were discussed.<sup>23, 254, 320, 485</sup> Special technic and especially careful interpretation are

required to demonstrate smaller lesions such as those of facets and of intervertebral foramina.

TABLE II  
CAUSES OF LOW BACK PAIN

(Ghormley<sup>253, 254</sup>)

(McDeed<sup>458</sup>)

1. Posture:
    - (a) Chronic postural strain:
      1. Lumbosacral or sacro-iliac lesions
  2. Trauma:
    - (a) Trauma involving vertebrae:
      1. Fracture
        - (a) Bodies
        - (b) Pedicles—may produce spondylolisthesis
        - (c) Laminae
        - (d) Facets
      - (b) Trauma involving joints:
        1. Traumatic spondylosis
      - (c) Trauma involving disks:
        1. Narrowing of disk
        2. Avulsion of disk
        3. Rupture of nucleus pulposus
  3. Infection:
    - (a) Arthritis, infectious
    - (b) Spondylitis deformans or *spondylose rhizomélisque*
    - (c) Fibrositis
    - (d) Typhoid spine
    - (e) Tuberculosis, etc. (real localized infections)
  4. Metabolic and senescent conditions:
    - (a) Hypertrophic changes (may be traumatic)
    - (b) Osteoporosis with pathologic fracture
  5. Congenital anomaly:
    - (a) Spina bifida
    - (b) Sacralization of fifth lumbar vertebra or lumbarization of first sacral vertebra
    - (c) Anomalous facets (may produce spondylolisthesis)
  6. Neoplastic conditions:
    - (a) Benign tumors:
      1. Osteoma and osteochondroma
      2. Giant cell tumor
      3. Hemangioma
    - (b) Malignant tumors:
      1. Metastatic from prostatic and mammary carcinoma, etc.
      2. Myeloma
      3. Primary osteogenic sarcoma
      4. Ewing's tumor, etc.
  7. Neurologic conditions:
    - (a) Tumors of spinal cord, etc.
1. Inherent normal variations.
    - A. Transitional types of vertebrae
    - B. Jointed { transverse processes  
articular processes
    - C. Asymmetrical joints
    - D. Incomplete closure of neural arches
    - E. Wedge-shaped vertebrae
    - F. Synostosis of vertebrae
    - G. Styloid processes at bases of transverse processes
    - H. Variations in shape and position of transverse processes
  2. Acquired.
    - A. Scoliosis
    - B. Traumatic arthritis
    - C. Herniation of nucleus pulposus into body of vertebra (due to faulty posture)
  3. Traumatic.
    - A. Fractures, or
    - B. Dislocations of bodies or accessory parts
  4. Disease.
    - A. Causing destruction
      1. Tuberculosis
      2. Malignant new growth
        - (a) Carcinoma
        - (b) Sarcoma
        - (c) Myeloma
      3. Destructive benign tumors
      4. Osteomyelitis
    - B. Producing new growth
      1. Osteomyelitis (destructive or constructive)
      2. Arthritis
      3. Syphilis
      4. Benign tumor
        - (a) Osteochondroma
        - (b) Osteoma
        - (c) Myositis ossificans traumatica
        - (d) Osteitis deformans (Paget's disease)
        - (e) Exostosis
    5. Disease of uncertain etiology
      - (a) Rachitis
      - (b) Chondrodysplasia
      - (c) Osteogenesis imperfecta
      - (d) Osteomalacia
      - (e) Osteitis fibrosa cystica, etc.

*Backache from Urologic Lesions.* Diseases of the kidney and upper urinary tract usually produce acute or chronic "high backache," generally unilateral, occasionally central or bilateral, often with pain referred to scrotum. Lesions of the prostate and urethra generally produce perineal



pain, less commonly low back pain.<sup>14, 253, 589</sup> Diagnosis rests on the appearance of localizing symptoms and on results of urologic examination.

*Backache from Gynecologic Lesions.* The pelvis should be carefully examined in all cases of backache and sciatica<sup>253, 616</sup>; however, gynecologic lesions are not common causes and uterine displacements per se have little or no relation to backache, according to Mercer. Backache due to gynecologic lesions is more likely to be exaggerated during menses than that due to skeletal disease. Back pain from intrapelvic tumors is likely to be chronic and intractable with little or no intermittency.<sup>612</sup>

*Backache and Sciatica from Postural Abnormalities.* Characteristics of this syndrome were reviewed by Mercer and Wesson. Correction of posture by postural and gymnastic exercises relieves the condition.

*Backache Due to "Functional Decompensation."* This is the commonest type of low back pain, according to Hauser. An imbalance exists between the functional capacity of a back and the demands made on it, producing chronic fatigue; sore, stiff, back muscles; aching pain low in the back; sometimes sciatica; an increase of all normal spinal curves. Roentgenograms are negative until secondary changes occur. Treatment was outlined: rest, physical therapy and the use of certain exercises (described) to restore normal posture, muscle strength and reserve capacity.<sup>302</sup>

*Backache from Senile Osteoporosis.* The condition, described by Ghormley, affects many more females than males, usually but not always more than 50 years of age. Pain may be severe and is usually of the "static type," relieved by rest, worse after activity. Roentgenograms show general spinal osteoporosis, sometimes pathologic fractures and ballooning of intervertebral disks as the expansile strength of disks takes advantage of the weakened vertebral bodies. The cause is unknown: Blood calcium and phosphorus are normal in this condition; they may be low in osteomalacia, and pelvic and other bones are affected in addition to the spine. Treatment included the use of a Taylor brace, a diet high in calcium and vitamins, tribasic calcium phosphate 4 gm. t.i.d.; and adult doses of vitamin D (cod liver oil, haliver oil, viosterol). Treatment must be prolonged; improvement rarely occurs in less than three to four months [or longer.—Ed.]

*Backache and Sciatica from Tight Fascia Lata and Iliotibial Band.* Ober again discussed this condition. Patients so afflicted are uncomfortable lying on their backs or abdomens, and generally they lie on their sides with knees flexed. According to Ober, signs of abduction contracture are generally but not always present (positive Ober test), straight leg raising is limited, and roentgenograms are negative. Kimberley did not consider Ober's test diagnostic of this condition. Before recommending fasciotomy Myers differentiates between organic and spasmodic contracture of iliotibial bands by the use of a general anesthetic; this will not relieve organic contractions. Results of fasciotomy were noted: Of 415 patients so treated relief was complete in 75 per cent, partial in 4 per cent, absent in 21 per cent (Ober). Smith treated 49 patients who had sciatica and tight fascia lata

and iliotibial bands. Of 20 treated by fasciotomy alone results were excellent or good in 75 per cent of cases, failure in 25 per cent; in 20 treated first by lumbosacral fusion, later by fasciotomy for persistent sciatica, results were excellent in only 20 per cent of cases, good in 5 per cent, poor in 75 per cent; of nine patients treated by fusion and fasciotomy six were completely relieved, three unrelieved. Fasciotomy in selected cases was approved without detailed comment by Ghormley, Myers and Smith.<sup>628</sup> Others found it difficult to select which patients will respond favorably and considered the rationale of fasciotomy unexplained.<sup>375, 451</sup> Kimberley considered it often very useful but less so than fusion.

*Relation of Piriformis Muscle to Sacro-Iliac Backache and Sciatica.* The piriformis muscle originates in part from the capsule of the sacro-iliac joint and is closely related anatomically to the sciatic nerve; the latter is found to pierce the muscle of 10 per cent of cadavers. When a sacro-iliac joint is diseased the piriformis muscle may be in spasm or actually diseased; in certain cases this may produce hyperemia of the sheath of the trunk of the sciatic nerve and may produce sciatica; such is Freiberg's concept. Myotomy of the piriformis muscle may give relief in such cases. Freiberg believes that results from Ober's fasciotomy may be accomplished by release of pressure on a piriformis muscle and sciatic nerve.

*Backache from Developmental Anomalies.* Studies on the incidence and significance of developmental anomalies in the lower back were reported.<sup>130, 375, 379, 725</sup> As causes of low back pain and sciatica they are much less important than lesions secondary to diseases of intervertebral disks.<sup>379, 721</sup> Of Williams' 400 cases, low back pain in 71 per cent presumably was due to disease of intervertebral disks; in only 29 per cent to vertebral anomalies. Such anomalies may be present without clinical significance.<sup>254</sup> However, Hodges and Peck considered them significant causes of sciatica: they were present in 27 per cent of 447 cases of low back pain and sciatica, but only in 14 per cent of 538 cases of low back pain *without* sciatica.

*"Facet Syndrome" (Acute Traumatic Subluxation).* Nine cases of this syndrome described by Ghormley (1933) were discussed by Troedsson. Characteristic was the sudden onset of low back or sciatic pain after some activity, often trifling, involving a twisting or rotary strain of the lumbosacral region. Muscle spasm and sciatic scoliosis may ensue. It is difficult for patients to bend forward, sit down, stand up or remove shoes. Pain is of variable severity and may persist until muscle spasm subsides or until surfaces of facets change their position by active or manipulative movement. Roentgenograms in ordinary positions are generally negative; disease of facets is best, or only, shown in oblique views. Pathologic reactions found in facets were generally those of traumatic (not infectious) arthritis: fibrillation and degeneration of cartilage and eburnation of underlying bone.<sup>254</sup> Troedsson assumed the presence of a minute subluxation of one or both inferior articular processes of the fifth lumbar vertebrae in his nine cases: simple manipulation without anesthesia was uniformly successful.

*Syndromes Resulting from Disease of Intervertebral Disks.* According to current writers most cases of pain in neck or low back, or sciatica are not due to "arthritis" of the spine but are secondary to alterations in intervertebral disks and are rather late manifestations of "discogenetic disease." The commonest site of these lesions is in the lower cervical and lower lumbar region. Their pathogenesis was clearly outlined by Oppenheimer and Turner and by Williams in an excellent series of papers illustrated by diagrams and roentgenograms. Features of discogenetic disease of the cervical region are less well known than those of the lumbar region. Of 72 patients referred to Oppenheimer<sup>508</sup> for "arthritis or rheumatism" of neck and shoulders only one had arthritis, 66 had narrowed cervical intervertebral foramina from discogenetic disease, three had cervical ribs; in two cases roentgenograms were negative. Symptoms in the cases of Oppenheimer and Turner were those of segmental neuritis: pain in shoulder girdle, between shoulder blades, over precordium, *rarely in the neck*; weakness and sometimes atrophy of shoulder muscles. The following train of events was noted: Constantly present was "primary" thinning of intervertebral disks (i.e., thinning not due to nuclear prolapse) which produced a narrowed intervertebral space. The cause of the thinning was generally assumed to be acute or chronic trauma from injury or faulty posture; many patients habitually stretched their necks forward. The narrowing of the intervertebral spaces produced subluxation of articular facets, but actual primary arthritis of facets was practically never noted (only once in 50 cases). The displacement of articular facets constricts the cervical foramina, demonstrable in oblique roentgenographic views; pressure on nerve roots results. Sometimes additional effects of the narrowing of intervertebral disks were noted; vertical (not posterior) nuclear prolapse; formation of exostoses on the anterior and lateral borders of the vertebral bodies. The exostoses are often said to be evidence of "hypertrophic arthritis" but are really not arthritis, as the intervertebral space is not a joint but a synchondrosis. The pressure on nerve roots cannot be caused by exostoses in these positions, and segmental neuritis was noted, even without such exostoses. In these cases Oppenheimer and Turner noted no loss of cervical flexibility as a whole, for this is not disturbed as long as four or more disks remain normal. In each case there was exact correlation between the segmental neuritis and the cervical disks affected.

*Symptoms Due to Narrowed Intervertebral Foramina.* Syndromes resulting from constriction of intervertebral foramina at various spinal levels were discussed in detail by Mooney and Willis but especially by Oppenheimer. The size of the foramina may be reduced by (1) collapse or (2) constriction of foramina. Collapse of intervertebral foramina may result from softening of intervertebral disks (from trauma), from rarefaction of articular processes (a rare condition of unknown etiology, occasionally affecting the pedicle of the sixth cervical vertebra), or from disease of vertebral bodies ("discogenetic disease"). Collapse of foramina begins

at anterior margins of foramina and may produce "hypertrophic arthritis" (vertebral exostosis). Constriction of foramina generally results from inflammatory swelling of synovial membranes of apophyseal joints of the spine followed by calcification of ligaments and ankylosis of facets (i.e., "spondylarthritis ankylopoietica"; rheumatoid arthritis of apophyseal joints). In these cases constriction begins at the posterior margins; disks are not involved and segmental neuritis is less common since the size of foramina is less reduced than in cases of discogenetic disease with collapse of foramina.

*Treatment of "Discogenetic Disease" and Narrowing of Intervertebral Foramina without Nuclear Prolapse.* Oppenheimer recommended head traction and neck stretching (Hanflig 1936) for cervical lesions, lumbosacral fusion for low back lesions. Williams reduced lumbosacral lordosis and restored the size of foramina by the use of a plaster of paris jacket; later, postural exercises and a "lordosis brace" worn six to 12 months. If these measures failed he advised lumbosacral fusion and facetectomy but only in cases of low back pain with segmental symptoms.

*Backache and Sciatica from Posterior Prolapse of Disk or Nucleus Pulposus.* This syndrome was further clarified in the excellent reports of Barr, Hampton, Mixter and Robinson and of Love and Camp. Vertical prolapse of disks is more likely to occur after severe trauma; horizontal (posterior) prolapse is more likely to result from less severe, even mild trauma received when the spine is in flexion.<sup>428, 616</sup> The factor of trauma was present in 60 to 80 per cent of the cases of posterior prolapse seen by Barr, Hampton and Mixter. Often shortly thereafter, pain appears. The prolapse may produce low backache or lumbago like that from many other causes, or root pain (especially sciatic) may be present, usually unilateral and often intractable. Pain is accentuated by coughing or sneezing or by whatever increases intraspinal pressure. Partial or complete remissions of pain are common. Numbness, tingling or weakness of a leg may be present; in severe and late cases, paralysis of an extremity or of sphincters may occur.<sup>34</sup> But often (in 50 per cent) neurologic symptoms and signs are absent except perhaps for diminished Achilles tendon reflex and a positive Laségue sign on the affected side. Decreased lordosis is usually present, sometimes sciatic scoliosis or kyphosis. None of these physical, neurologic or orthopedic signs is specific for this syndrome. Of the patients of Love and Camp, four had pain in neck or upper extremities, 26 had low back pain with sciatica, 11 had sciatica only, four had low back pain without sciatica; symptoms averaged 1.4 years before diagnosis was confirmed by operation.

Preoperative diagnosis depends on visualizing a filling defect in roentgenograms after injection of lipiodol, but since lipiodol may occasionally have irritating properties, cases for such injections are selected by preliminary tests. If a patient with low back pain and sciatica presents the neurologic symptoms and signs noted, the spinal fluid is examined and a

Queckenstedt test (for subarachnoid block) is made; the latter is generally negative but is of great significance if positive. Love and Camp considered of great significance the presence of a positive "reverse Queckenstedt test"—the duplication or exaggeration of low back pain or sciatica during the injection of 1 per cent procaine solution into the caudal epidural space. The spinal fluid protein is generally (in 75 per cent) increased (more than 40 mg. per 100 c.c.). It was increased in 52 of 58 cases of Barr, Hampton and Mixter; in 30 of 41 cases of Love and Camp; in the latter's cases it varied between 20 and 360 mg. per 100 c.c. A normal concentration of protein in spinal fluid does not rule out prolapse of a disk. One should obtain fluid as low in the spine as possible and examine the first 2 to 5 c.c. collected; otherwise the protein may be normal. If the reverse Queckenstedt test or the spinal fluid protein test, or both, are positive one is justified in injecting lipiodol for the demonstration of filling defects. Before this is done, however, some make an "aerogram," a caudal roentgenogram after injection of air; if this is normal, some consider injections of lipiodol not indicated.<sup>616</sup> Ordinary roentgenograms are generally normal or at least of little significance; narrowing of disks may be apparent but often does not coincide with the symptom-producing lesion, hypertrophic changes are likewise of no localizing value. The technic and interpretation of roentgenographic studies with lipiodol were clearly described by Hampton and Robinson, by Barr, Hampton and Mixter, and by Love and Camp. No less than 5 c.c. of oil should be injected; smaller amounts proved unsatisfactory. Such studies were "90 per cent accurate" in the hands of those mentioned. No false positives were noted. [Occasional "false positives" have since been encountered.—Ed.] Therefore laminectomy should not be performed if such studies are negative. The great value of such studies far outweighs the slight risk of producing irritation; in more than 100 cases no permanent ill effects were noted (Hampton and Robinson).

Treatment. Prolapsed disks may be discovered at levels unrelated to symptoms; unless symptoms of pressure on the cord or spinal roots are present and unless the level of symptoms corresponds to the level of the lesion in roentgenograms, surgical treatment is not indicated. Relief, usually prompt and complete, results from laminectomy and removal of the protruded material. In the 50 cases of Love and Camp, lesions were lumbar in 38 (multiple protrusions in six), thoracic in seven, cervical in five cases. Results were complete relief in 33, partial in 15, none in two; there were no postoperative deaths. Among 58 cases Barr, Hampton and Mixter noted these results: complete relief in 32, partial relief in 12, no relief in two, results too recent to evaluate in eight; one postoperative death, three later incidental deaths. Love and Camp did not advise the use of bone grafts or the postoperative use of braces or casts; Barr, Hampton and Mixter occasionally advised bone graft after laminectomy if patients were

doing heavy work. Excellent results from laminectomy were noted in six cases of others.<sup>98, 616, 620, 625</sup>

*Low Back Pain and Sciatica from Hypertrophy of Ligamenta Flava.* These ligaments connect the laminae of contiguous vertebrae, blend with interspinous ligaments and help to form the capsules of joints between articular facets; the lateral edges of these ligaments form the posterior margin of intervertebral foramina. At times they increase in thickness so that they encroach on the spinal canal and compress the cord at any level but especially at the fourth and fifth lumbar vertebrae. Spurling, Mayfield and Rogers, and Brown<sup>81</sup> reported 14 such cases. Symptoms were similar to those from protruded disks: chronic low back pain, after trauma, generally with sciatica, sometimes numbness of leg or buttock, muscle atrophy or weakness, postural deformity, diminished or absent Achilles tendon reflexes; complete spontaneous remissions may last a few weeks to several years. Roentgenograms by ordinary technic reveal nothing significant; those after injections of lipiodol reveal filling defects. Treatment consisted of removal of involved laminae and ligaments; results should be as satisfactory as those from removal of protruded disks.<sup>81</sup> Of seven patients so treated, prompt relief was noted in six; there was one postoperative death.<sup>647</sup>

*Treatment of Low Back Pain and Sciatica: General Comments.* Obviously low back pain and sciatica arise from infinite causes; sciatica is merely a name for a regional pain caused chiefly by injury or infection. Among other infections, undulant fever may cause sciatica.<sup>19, 222</sup> Reduced skin temperatures in affected legs suggested to Eldbloom and Ingvar that ischemia may be a factor in sciatica; vasodilators were used in treatment. All patients with sciatica deserve neurologic examination.<sup>254</sup> In certain cases of sciatica, roentgenotherapy seemed valuable<sup>325, 354</sup>; short wave therapy seemed useful to some,<sup>570</sup> useless to others.<sup>355</sup> Sulfanilamide is not indicated.<sup>714</sup> Symptoms and treatment of sciatic scoliosis were noted by Kleinberg, Watson-Jones, and Levine; the latter reviewed 80 cases. Rest in bed, physical therapy, and belts were used in mild cases; traction, caudal block, plaster jackets, injections into the sciatic nerve in severe cases; fusion operations in intractable cases. Manipulation of the spine under anesthesia was used by some, disapproved by others.<sup>254, 325</sup> Wardle relieved 26 patients by fixation in "head suspension plasters."

When the cause of low back pain or sciatica in a given case is not clear, rather than advising surgical procedures physicians should use conservative methods and allow time to clarify the diagnosis.<sup>612</sup> Measures recommended in acute cases were rest in bed, a firm mattress, use of Bradford frame or "fracture bed"<sup>250, 254, 287, 375, 470, 518</sup>; head or pelvic traction if much muscle spasm was present<sup>250, 470</sup>; use of a small pillow under the lumbar region<sup>470</sup> or a scultetus bandage<sup>254</sup>; adhesive supports are only occasionally applicable as physical therapy is more important. In ambulatory cases supports of one sort or another, physical therapy and graded exercises, especially swimming, were advised.<sup>254, 470</sup> In resistant cases some

used rest in bed, traction, lumbar supports and physical therapy<sup>254</sup>; others used epidural injections<sup>250, 489</sup>; Kimberley believed the latter useless. Manipulations in selected cases were approved by some<sup>250, 327, 451, 470, 489</sup> who described various methods; manipulation was disapproved by others.<sup>375</sup>

*Indications for Fusion Operations.* Those of Ghormley and Wesson were (1) persistent low back pain with or without sciatica, (2) failure of conservative therapy, (3) presence of narrowed lumbosacral disk or facet changes or both, (4) negative neurologic examination, (5) consistently localized tenderness, (6) static type of pain (if rest won't give even temporary relief, fixation will not help); (7) patients aged 20 to 50 years. In such cases results from various types of fusion were satisfactory in a high percentage. Compere listed contraindications for fusion: (1) low back pain with infectious arthritis, (2) unsettled compensation cases, (3) elderly or "poor-risk" patients, (4) girls before puberty. Compere preceded fusion operations with vigorous stretching and manipulation. A conservative attitude toward fusion is required. Among 139,000 patients at the University of Chicago clinics were 2242 with low back pain; only 76 patients (3.4 per cent) were subjected to fusion (Compere).

*"Platyspondylia Aortosclerotica."* This term was applied by Oppenheimer to a syndrome "not found described." Six patients presented marked calcification of the thoracic and abdominal portions of the aorta with a systemic spinal disease characterized roentgenographically by demineralization of vertebral bodies, collapse of midthoracic and upper lumbar bodies, pronounced expansion of intervertebral disks into softened vertebrae. Other parts of the skeleton were unaffected, apophyseal joints of the spine and intervertebral foramina were free. In the longitudinal ligaments sometimes there were small calcifications. There were no signs of metabolic or endocrine disorders, or of peripheral or cerebral arteriosclerosis. Except for the gradual formation of a gibbosity the disease did not cause marked subjective symptoms.

[To us these cases represent, not a new disease but senile osteoporosis with coincidental aortic sclerosis.—Ed.]

*Spinal Malignant Growths and Other Lesions.* Malignant neoplasms must always be considered if progressive low back pain is unrelieved even temporarily or partially by ordinary measures. Early cases of malignant disease coincidentally associated with developmental anomalies or "hypertrophic arthritis" of the spine are especially likely to be missed.<sup>187, 254, 458</sup> Features of some unusual spinal lesions were described: hemangioma<sup>255</sup>; vertebral osteomyelitis with infection of epidural spaces.<sup>77</sup>

*Post-Traumatic Neurosis of Spine.* A post-traumatic neurosis often represents "a protest of labor against capital."<sup>234</sup> In such cases symptoms may resemble those due to organic change (muscle spasm, abnormal posture and gait, hypertrophic changes) but neurologic signs and muscle atrophy are generally absent, or unphysiologic areas of anesthesia are present, and

patients respond to placebos and psychotherapy; electricity, simple injections and supports are used as media for the latter. Some patients cling to their braces even at night: "Their brace supports their claims more than their vertebral column. . . . Physicians must look beyond the back to the background" which is often that of a person dissatisfied with work or with life, at conflict with reality (Fetterman). [A diagnosis of post-traumatic neurosis should be made only with the greatest care. Most cases of backache are caused by real organic or functional disability.—Ed.]

"*Spine Malingerers.*" Consistently localized tenderness is of great help in distinguishing organic disease from malingering. Most experienced examiners can tell whether a patient's response to percussion or palpation is overdone or feigned. Malingerers never time their responses accurately; they are usually too quick, sometimes too slow. Their attitude in other ways is often characteristic of the "compensation neurotic" and gives them away (Ghormley).

### SPONDYLITIS

Two types were again described: (1) atrophic spondylitis (spondylitis ankylopoietica) and hypertrophic spondylitis (spondylitis osteo-arthritis) corresponding respectively to atrophic and hypertrophic arthritis in other regions. Scott noted three types: (1) "spondylitis adolescens" (spondylitis ankylopoietica), (2) spondylitis osteo-arthritis, and (3) spondylitis as a late manifestation of "infective polyarthritis." In the first type "sacroiliac joints are always abnormal"; in the latter two types "sacroiliac joints are always normal," according to Scott.

*Atrophic Spondylitis (Spondylitis Ankylopoietica).* The usual clinical and roentgenographic features were described.<sup>263, 406, 605, 689</sup> A case with prominent neurologic symptoms was described (Ziskind and Ziskind). The disease was regarded as the spinal equivalent of atrophic (rheumatoid) arthritis by some<sup>39, 689</sup>; as a different disease by others.<sup>169, 263, 605</sup> If it is the same as atrophic arthritis (which affects females more than males) why does atrophic spondylitis affect males from four to 14 times as often as females? Scott again elaborated his thesis (reported in previous Reviews) that the first demonstrable lesion is always in sacro-iliac joints, presumably infectious, bilateral sacro-ileitis which long antedates the spinal symptoms of "spondylitis adolescens." No organisms had been recovered from sacro-iliac joints, however. According to Buckley,<sup>85</sup> Scott's thesis has not yet been proved: "One meets with cases occasionally with typical ankylosing changes in the upper spine in which the sacroiliac joints are not affected till later." Oppenheimer,<sup>507, 508</sup> who regarded this disease ("ankylosing spondylarthritis") to be atrophic arthritis of apophyseal joints, stated that by newer roentgenologic methods (described) for visualizing facets and foramina one can generally note involvement of lower thoracic apophyseal and costotransversal joints, sometimes several years before sacro-iliac involvement.



**Treatment.** Scott advised early search for the sacro-iliitis among young persons with wandering back and thoracic pains, and repeated wide-field roentgenotherapy. Results were not given but were presumably satisfactory. However, Gordon considered "deep x-ray therapy," foreign proteins and vaccines "absolutely contraindicated." The usual measures were recommended: rest in bed, plaster support, hyperextension frames, postural and deep breathing exercises, nutritious diet, removal of foci of infection.<sup>263, 406, 507, 689</sup> Hartfall, Garland and Goldie gave chrysotherapy in 18 cases: there was "marked improvement" in five, no patients were cured. Gold, fever therapy and vaccines were "disappointing."<sup>689</sup>

*Hypertrophic Spondylitis (Spondylitis Osteo-Arthritica).* The current concept is that this is not true arthritis but spondylosis, only an exostotic reaction to mechanical irritation arising from alterations in vertebral bodies and in intervertebral disks. In hypertrophic spondylitis disks and vertebral bodies are frequently narrowed; in atrophic spondylitis disks are not narrowed.<sup>263, 507</sup> Osteo-arthritis is not a common cause of low back pain with sciatica, according to Hodges and Peck: it was present in 24 per cent of 447 cases of backache with sciatica, but also in 28 per cent of 538 controls without sciatica. Of 529 cases of hypertrophic arthritis of various joints, studied by Kuhns, the spine was the cause of symptoms in 294 cases (195 females; 99 males). Average age of the 294 patients was 53 years: 11 patients were 30 to 40 years old; one woman of 28 years, a professional dancer, had marked lumbar hypertrophic changes. In three cases there was coincidental metastatic carcinoma, a possible source of serious errors in diagnosis. Metabolic rates were subnormal in only 17 per cent. Symptoms were exaggerated by trauma, also by intercurrent infection, e.g., colds. Gillespie noted a case with marked cervical hyperextension and neurologic manifestations simulating amyotrophic lateral sclerosis. Fibrositis is a common accompaniment of hypertrophic spondylitis (Gordon).

**Treatment.** The usual methods were advised: rest if necessary in a plaster shell, supports, physical therapy. Roentgenotherapy seemed useful to Kahlmeter. Head traction was approved by Oppenheimer; slight, but not forceful or manipulative, traction was approved by Kuhns. Of the latter's 294 patients, 70 per cent were able to work, 18 per cent were not, 12 per cent had died.

[Follow-up period unstated.—Ed.]

#### GOUT AND GOUTY ARTHRITIS

*Clinical Features.* Acute gout is less common and less severe than formerly, according to some<sup>846, 553</sup>; it is common but frequently misdiagnosed according to others.<sup>310, 590</sup> The features of typical gout and gouty arthritis were reviewed by Buckley, Copeman, Graham, Hench, Jennings, Rutledge and Bedard, and Volini. The classical pattern of gouty arthritis was generally accepted as being one of recurrent attacks of acute gouty arthritis with complete symptomatic remissions, later, in some cases, chronic

gouty arthritis. The tendency for acute attacks to be seasonal in appearance and consistently related to certain provocatives was well illustrated in a case reported by Rutledge and Bedard: 13 acute attacks were experienced in nine years; of these attacks seven were provoked by the feasting of Christmas-New Year week, three by seasonal occupational trauma, one by other trauma, one by an operation (another attack made worse by an operation), one by no known factor. Of 19 diagnostic features of gout this patient illustrated 13. The clinical features considered by Hench as points useful in the diagnosis of presumptive (pretophaceous) gout were reviewed by Rutledge and Bedard. The tendency for gouty arthritis to involve the more peripheral joints and rarely to affect spine, shoulders and hips was noted.<sup>310</sup> Typical gout is reputedly rare among Chinese: A case of tophaceous gout was reported.<sup>479</sup> A patient of Owen and Roberts with acholuric (hemolytic) jaundice developed recurrent acute gouty arthritis presumably related to excess nucleoproteins from destroyed erythrocytes; splenectomy was performed and both conditions disappeared.

[On the seventh postoperative day acute gouty arthritis occurred. One of us, P. S. H., noted (1935) the frequency and diagnostic importance of acute postoperative gouty arthritis.—Ed.] Garrod's theory that gout results from renal insufficiency has generally been abandoned; renal insufficiency may result from gout but few believe that gout is a symptom of nephritis. Copeman noted a man with tuberculous calcification of both kidneys; progressive renal insufficiency, uremia and hyperuricemia occurred; subsequently two attacks of gouty arthritis, a disease previously absent.

[The relationship may have been coincidental, not etiologic.—Ed.]

Cases of unquestioned (tophaceous) gouty arthritis in which the arthritis comes on insidiously and progresses chronically without complete remissions occur rarely if at all; however, Buckley and Copeman accepted as gout certain cases of arthritis, chronic from the onset, associated sometimes with hyperuricemia (but no tophi) and somewhat relieved by a regimen for gout. [In such cases the hyperuricemia, in our experience, is often due to coincident mild arteriosclerotic nephritis, is not due to gout and is not related to the arthritis.—Ed.]

Several writers continued the argument on the existence of "irregular gout." Pringle spoke of plethoric gout and gouty glycosuria, eczema, phlebitis or bronchitis. The gouty nature of most of these complaints was denied by Buckley, Copeman and Graham and by the majority of Americans interested in gout.<sup>310</sup> However, the authenticity of gouty eczema was entertained by Copeman, that of gouty phlebitis by Buckley. [One of us, P. S. H., recently saw acute phlebitis in a gouty patient; biopsy of the vein revealed no urates therein and measures successful in gouty arthritis did not affect the phlebitis.—Ed.] Acute or chronic "gouty fibrositis" (fasciitis, lumbago, sciatica) was considered by some an accepted feature of the disease amenable to the usual measures for gout.<sup>87, 148, 346</sup>

*Laboratory Data.* Sedimentation rates in Jennings' eight cases of acute gouty arthritis ranged from 60 to 100 mm. (1 hour; Westergren method). Arneith counts and glucose tolerance tests were normal in Kersley's cases

(no details). Hyperuricemia is generally but not always present, and may be absent even during an acute attack<sup>87, 272, 346, 590, 690b</sup>; its relationship to gout is now usually regarded as of secondary, not of etiologic, importance.<sup>148, 310</sup>

*Etiology and Pathogenesis.* The usual ideas were expressed by several.<sup>87, 148, 690b</sup> The opinions of various American specialists were reviewed by Hench.

1. Metabolic factors: The uric acid problem. Gout is commonly defined as a disturbance of purine metabolism. Thus Pringle considered it "an error of metabolism in which the liver is the chief offender." However, some, among them Thannhauser (1932), insist that it is not a true metabolic disease; that in gout there is no disturbance of intermediary purine metabolism but an obvious disturbance in the disposition of uric acid; apparently the kidneys of gouty patients simply cannot concentrate and eliminate urates adequately even though they handle other metabolites satisfactorily. Thus, to them gout is not a metabolic disease but some peculiar type of selective renal insufficiency. Studies by Grabfield suggest that some functional disturbance of the vegetative nervous system, involving especially renal innervation, may cause gout.

It has been believed that cinchophen controls the excretion of uric acid by some direct action on renal epithelium but Grabfield and Pratt (1931) concluded from certain experimental data on humans that excretion of urates was accomplished by the action of cinchophen on the central nervous system. This conclusion has now been supported by animal experiments. Cinchophen and other drugs were given to dogs before and after denervation of kidneys. In most dogs a large part of the purines is reduced to allantoin, a small part to uric acid. Dalmatian hounds excrete much more uric acid than allantoin. In both types of dogs, before renal denervation, cinchophen increased the excretion of total nitrogen, allantoin and uric acid. After renal denervation the drug produced increased excretion of the first two but decreased excretion of urates. This reversal of the "uricosuric action" of cinchophen slowly disappeared as renal nerves regenerated. "Had the action of the drug been a simple one on the renal epithelium through its nerve, one would expect denervation to eliminate the action. However, the reversal of effect on the completely denervated kidney cannot be explained on any simple basis and must involve interaction either with some other organ or between the sympathetic or parasympathetic systems." Ergotamine in certain doses blocks sympathetic impulses. When ergotamine was given simultaneously with cinchophen to normal dogs the physiologic effect of cinchophen was cancelled by the ergotamine: the effect on excretion of uric acid was similar to that in the denervated kidney but there was also an elimination of the effect on the excretion of total nitrogen and allantoin (Grabfield, Prescott and Swan). Atropine in adequate doses will block parasympathetic impulses. The use of atropine with cinchophen did not modify the ordinary effect of cinchophen (alone) on urate excretion but eliminated the effect of cinchophen on allantoin excretion. Apparently the effect of cinchophen on allantoin excretion is mediated through the parasympathetics, that on uric acid excretion is mediated by the true sympathetics, and uric acid excretion may be modified by the autonomic nervous system.

Certain clinical observations were correlated with the foregoing. Harpuder (1924) noted that ergotamine reduced the excretion of urates by

normal persons, and Hench (1935) noted the provocative effect of gynergen (ergotamine tartrate) on gouty patients. [The provocative effect was inconsistent and unreliable as a (provocative) test for diagnosis.—Ed.] Grabfield noted a similar case and stated that Thannhauser had also seen precipitation of gout by ergotamine. In Grabfield's case the injection of ergotamine produced urinary diuresis, an absolute *increase* in uric acid excretion but a *reduction* in the urinary uric acid concentration; about seven hours after injection of the drug the patient's great toe became red and painful. These facts suggested that "the gouty attack and uric acid excretion do not necessarily run hand in hand; nevertheless they are both connected with the autonomic mechanism which controls the concentration of uric acid in urine."

2. Factor of allergy. The theory of Llewellyn (1927), Gudzent (1928) and others that acute gouty arthritis represents an allergic reaction to unknown food or bacterial allergens was favored by Buckley, Cmunst and Pringle but was not supported by new data. In America this theory finds little support.

3. Factor of infection. Infection is not the cause of gout but may provoke gouty arthritis.<sup>148, 272, 553</sup> Gout is not due to the local action of an infective agent but sodium biurate may be deposited in joints damaged by bacterial action.

*Treatment.* Accepted principles and methods of treatment were reviewed.<sup>87, 148, 272, 310, 346, 690b</sup> For acute attacks the following were recommended: an early purge; colchicine; purine free diet; antiphlogistic compresses; cinchophen or salicylates, or salicylates with amino-acetic acid; various types of physical therapy. Gouty patients always should have colchicine handy.<sup>272</sup> It was stressed that the indefinitely prolonged treatment of gouty patients after an attack may modify the disease greatly, and is more important than the treatment of acute attacks. Such "prophylactic" or "interval-treatments" included removal of foci of infection,<sup>148</sup> dietary restrictions of greater or lesser severity, the use of cinchophen or a substitute therefore. Spa therapy may help to prevent attacks but may actually precipitate attacks if injudiciously given at certain phases of gout.<sup>87, 148, 553</sup> Physicians differed in their attitude concerning alcoholic beverages. Some advised the avoidance of all of them; others considered certain forms rather harmless but there was no unanimity regarding the exceptions allowable. The treatment of coincidental infection of the urinary tract of gouty patients with ketogenic diets may provoke acute gout; mandelic acid therapy is preferable.<sup>143</sup>

[Sulfanilamide probably will supplant some of these remedies.—Ed.]

Cinchophen and substitutes. The comparative value of cinchophen and salicylates in gout was discussed in detail in the first Review.<sup>1</sup> Although salicylates augment excretion of urates they were considered less valuable than, and not a satisfactory pharmacologic substitute for, cinchophen. According to some only large irritating amounts of salicylates were effective in

gout. According to others, salicylates may actually provoke acute attacks.<sup>1</sup> Therefore, in spite of its occasional toxicity cinchophen has been used by those of greatest experience with gout; many<sup>310, 690b</sup> in America still prescribe it to be used intermittently for long periods somewhat after the plan of Graham (1920; 1926).

Graham's present method<sup>272</sup> of using cinchophen to prevent attacks follows: Cinchophen 15 grains t.i.d. first day of week, no medicines on second day, acetylsalicylic acid grains 10 t.i.d. on third to sixth day of week if pain persists, no medicine on seventh day; this weekly program to be continued indefinitely. To test a patient's tolerance to cinchophen Graham recommended for the first week one 15 grain dose only; for the second week two such doses; the third week three such doses one day a week. If hyperuricemia persists, cinchophen is given two days a week, 15 grains t.i.d. After severe attacks or in recurrent cases "cinchophen should be given for many months." Blood uric acid should be estimated every one or two months; if it approaches normal the dose of the drug is reduced or stopped temporarily.

Some patients fear, others do not well tolerate, cinchophen; others with hepatic dysfunction should avoid it. For such patients, unable to prevent acute recurrences by diet alone, Hench prescribed salicylates (60 grains) with (glycine) amino-acetic acid (150 grains) daily during attacks and intermittently thereafter. A synergistic action of salicylates and glycine was noted in normal persons by Quick (1933). This seemed to control symptoms and hyperuricemia in the case of Rutledge and Bedard.

[Hench's preliminary results with these drugs seem to indicate that they are effective both clinically and chemically in some cases, clinically (providing analgesia) but not chemically in others, chemically (controlling hyperuricemia) but not clinically in others. This is probably as should be expected for "hyperuricemia" and the disease "gout" are not synonymous. Its further use is justified but it is not a complete substitute for cinchophen.—Ed.]

According to Jennings salicylates alone (80 grains daily) are quite as effective as cinchophen (45 grains daily) in controlling pain and hyperuricemia. Their effects were studied in eight cases: two males with tophi, three males and three females with pretophaceous gout. [The presence of gout in two of the females seems debatable.—Ed.] Augmentation of urate excretion was actually somewhat greater from salicylates in six cases, from cinchophen in one case; one case was equally affected by both drugs. The total average daily urate excretion in the eight cases was 0.37 gm. without drugs, 0.52 gm. after atophan, 0.66 gm. after sodium salicylate. In two cases the blood urates were unaffected by atophan; otherwise both drugs consistently lowered blood uric acid. The total average blood uric acid concentration for the eight cases was 4.4 mg. per 100 c.c. before atophan, 3.1 mg. after atophan; 5.1 mg. before salicylates, 2.6 mg. after salicylates. The height of blood uric acid before use of a drug bore no fixed relationship to the amount of uric acid excreted after use of the drug or to the drop in the level of blood uric acid during its use; urinary urates were far in excess of amounts lost by blood; hence, much of the urates excreted under the

influence of these drugs must come from tissues, including tophaceous deposits. Jennings recommended prophylactic therapy to include sodium salicylate 80 grains daily, sodium bicarbonate 120 to 150 grains daily three to four days a week; it will control hyperuricemia and is free from serious toxicity.

*Cinchophen Toxicity.* Cinchophen was considered "a very important drug for which there is no substitute,"<sup>686</sup> "practically specific in many cases of chronic gout,"<sup>148</sup> "of great value between acute attacks of gout,"<sup>374</sup> "the most valuable in preventing attacks of gout and alleviating the chronic joint condition."<sup>272</sup> But it was also considered a dangerous drug, to be used with caution. [Some of us do not believe there is any method of giving cinchophen "with caution" since severe toxicity may result occasionally from small doses.—Ed.] Kersley noted "transitory jaundice" from one dose ( $7\frac{1}{2}$  grains) given for an unstated disease (gout?).

[It would be interesting to know this point because cinchophen toxicity has rarely been noted in gouty patients; there were only six cases of "gout" among the 191 cases of cinchophen toxicity reviewed by Palmer and Woodall, 1936.—Ed.]

Hench quoted the statistics of Bryce: The chances of fatal toxicity from cinchophen are about one in each 61,000 courses of treatment, a "typical course" being the use of  $\frac{1}{4}$  pound (0.1 kg.) per patient. Since statistics indicate that in uncontrolled gout the chances of gouty nephritis or other serious complications are at least 15 per cent or more, certain American students of gout [but not all.—Ed.] have felt justified in assuming the small risk from cinchophen to try, if possible, to prevent the serious, even fatal renal or vascular manifestations of gout as well as the progressive disability of gouty arthritis.<sup>310</sup>

[But those who assume the risk must face the facts and if it can be shown that salicylates, with or without amino-acetic acid, will effectively control gout it would be senseless to support the cause of cinchophen longer. One of us, W. B., believes that neither cinchophen nor any other treatment materially alters the course of gout or stops the progression of gouty nephritis once the latter has begun. Others of us believe that, in spite of our inadequate knowledge of gout, an attempt to control the hyperuricemia of gout is sound therapy even though hyperuricemia may be a secondary, not a primary, factor in the disease. However, none of us has final proof for or against these beliefs and further prolonged observations are in order.—Ed.]

Three new cases of cinchophen toxicity were noted: none were cases of gout. A patient with "pain in sacroiliac region for some weeks" took 70 to 80 grains of neo-cinchophen over a period of several days; there ensued marked hepatitis and jaundice (icterus index up to 195, van den Bergh up to 10); under treatment (large amounts of glucose, high carbohydrate diet, "liver poultice") the patient recovered completely.<sup>191</sup> Lyall noted two fatal cases of liver atrophy from atophan; a man with "rheumatism" for six weeks (finger joints stiff and sore) took 18 tablets (size unstated) within 14 days; a woman with "rheumatoid arthritis" for many years took an unstated amount of atophan.

Palmer, Woodall and Wang again reviewed the 191 cases of cinchophen toxicity reported in the literature; there were 88 deaths, mortality rate 47 per cent. In some cases toxicity, occasionally fatal, occurred from very small, carefully administered doses. In some cases the drug was given carefully, fearfully, and its administration was stopped promptly with onset of toxicity, yet death resulted. "This illustrates the futility of attempting to find a safe method of administration and of thinking that the drug can be given safely, if given cautiously, under observation." Often signs of toxicity first appeared long after administration of the drug was stopped. Occasionally it can be taken in rather large doses for a long period without apparent ill effects until suddenly jaundice appears; death may then rapidly ensue. Sex and age were not apparent factors; most patients did not previously have hepatic disease. The long time which may elapse between ingestion of the drug and onset of symptoms "speaks strongly against an allergic basis although the cutaneous reactions which appear promptly do seem to be of this type. It does not seem to be a question of idiosyncrasy but of variable susceptibility." To determine the incidence of toxic hepatitis with and without cinchophen, more than 3000 records of necropsy were reviewed; these included 21 cases of toxic necrosis and cirrhosis of liver, in at least six of which cinchophen had been taken for "arthritis."

In Scotland under the Poison Act (1936) atophan became a "Schedule 1 poison"; Lyall urged government control over all such preparations.

Some have been able, others unable to produce experimentally in animals toxic lesions from cinchophen. After dogs had been given variable doses of cinchophen (1 to 2 gm. daily) by various routes Stalker, Bollman and Mann noted no change in the level of gastric acidity but an increased amount of gastric secretion; this was followed in 96 per cent of animals by the development of ulcers, generally peptic, occasionally duodenal, then gastric hyposecretion. Formation of ulcer was prevented or modified by certain factors enumerated. No definite instances of cinchophen toxicity with ulcer formation have been noted in man.

#### PSORIASIS AND PSORIATIC ARTHRITIS

The literature on psoriatic arthritis and requirements for its diagnosis were briefly reviewed by Jeghers and Robinson who reported one case and summarized certain clinical characteristics of the disease.

Features of the case [the patient was a man aged 54 years] follow: psoriasis 15 years without joint lesions; then sudden marked extension of psoriasis with involvement of nails and changes in the character of the cutaneous lesions; malaise, chilliness, weakness, slight fever; a few weeks later onset of severe polyarthritis (knees, elbows, ankles, wrists, hands) which forced the patient to bed; roentgenograms showed periarticular swelling, slight bone atrophy and destruction, findings similar to those of atrophic arthritis. Ignoring the skin, joints were treated vigorously for six weeks without effect; treatment of joints was then abandoned, a diagnosis of psoriatic arthritis was entertained and the skin treated vigorously by Goeckerman's (1931) regimen. Skin and articular lesions cleared "completely" within a few weeks.

Jeghers and Robinson agreed that a diagnosis of true psoriatic arthritis depends mainly on the close relationship which exacerbations and remissions in skin may bear to those in joints. Psoriatic arthritis resembles atrophic arthritis in many ways but possesses certain distinctions: frequency of severe involvement of terminal joints of fingers and toes with psoriasis of adjacent nails (Brocq 1910, Hench 1935); articular remissions which are more frequent, rapid and complete than in ordinary atrophic arthritis and which may occur when skin clears spontaneously or under therapy. However, after several attacks or in severe cases joint lesions may take an independent or resistant course, ending in permanent damage. "The parallelism between the severity of the skin and joint lesions seems to support the theory that the arthritis is due to toxic products absorbed from skin lesions." Cases of psoriatic arthritis are too infrequently recognized: dermatologists tend to ignore the joints; internists ignore the skin. [One of us, W. B., recently noted a case of chronic polyarthritis with psoriasis in which cinchophen toxicity induced a complete remission of the arthritis but not of the psoriasis.—Ed.]

Among 231 cases of psoriasis Lane and Crawford noted 74 (32 per cent) with "arthritis"; of these 14 had "psoriatic arthritis" (simultaneous onset or synchronous aggravation of skin and joint lesions). Characteristic nail changes were present in fingers in half of the cases; in toes in a fourth. In all cases with involvement of toe nails, finger nails were also affected. [No note was made on the terminal phalangeal joints.—Ed.] A variable (generally beneficial) effect of pregnancy on psoriasis was seen. Among 19 cases of "rheumatoid arthritis" in which psoriatic lesions were present Dawson noted seven which some might have called true psoriatic arthritis. Less than 2 per cent of patients with rheumatoid arthritis develop psoriasis. Dawson reached no conclusion as to the validity of the entity. Brief reviews of current theories on causation and methods of treatment of psoriasis were made (without comment on joints) by Orr and by Oliver and Crawford. Some associate psoriasis with faulty lipid metabolism and increases of certain blood fats. Rosen, Rosenfield and Krasnow noted low rather than high values for blood cholesterol, but changes were slight and they could not postulate a disturbance in lipid metabolism in psoriasis.

The preliminary effects on psoriasis of massive doses of vitamin D and ergosterol were noted by Ceder and Zon. Of 15 patients with psoriasis [joints not mentioned] given 300,000 to 400,000 units daily for several (up to 12) weeks, the skin of 11 cleared completely, that of two partially; two patients were not benefited. All developed transient hypercalcemia (12 to 16 mg. per cent); several noted mild, transient toxicity. [May not such degrees of hypercalcemia be potentially dangerous?—Ed.] The treatment was "practical, simple and effective." Colloidal manganese was considered of value by some<sup>505</sup> but not by others.<sup>500</sup> Some recommended autochemotherapy.<sup>30, 330</sup> Intravenous injections of typhoid vaccine are frequently used for psoriasis; such an injection after three preliminary subcutaneous doses



was followed, in a case of Rosen, by an unusual reaction: edema, erythema, renal and hepatic damage; the patient responded to intravenous injections of 10 per cent glucose.

### HEMOPHILIA AND HEMOPHILIC ARTHRITIS

Brief reviews of current opinions on the pathogenesis and treatment of hemophilia appeared<sup>213, 433, 516, 665</sup> but no new studies on hemophilic arthritis. A few cases of hemophilic arthritis were mentioned.<sup>213, 665</sup> Hemophilia in negroes is extremely rare; three cases, two with typical genealogical charts, were noted by Pachman; one had arthritis.

Although Birch's hypothesis was endorsed by some,<sup>665</sup> Eley considered the theory unproved and ovarian substances of debatable value. Theelin therapy was followed by improvement in one of Pachman's cases. Eley discussed further the value of the anticoagulant extract from human placentas developed by Eley, Green and McKhann (1936). In 12 of 19 hemophilic children, given the extract orally or intramuscularly, normal blood coagulation resulted; a later report noted favorable results in 13 of 20 cases.<sup>212, 213</sup> The effect persists only 48 to 78 hours. Intravenous injections of the extract may prove fatal. In certain cases the extract was valueless. It seemed of value in two of Pachman's cases. Clots formed by this extract in vitro and in vivo were studied.<sup>460</sup> Addition of the extract to plasma of hemophiliacs increased the coagulation time and caused the formation of large, firm, slowly retractile, hydrophilic clots. Hemophilic patients who received the extract orally obtained reduced coagulation time of blood and improved blood clotting but in no instance were clots entirely normal.

Normal, fresh plasma and serum contain a coagulation-promoting substance of uncertain identity; it is present in the protein fraction but is not euglobulin. Bendien and Van Crevald described methods for its separation. It was given intravenously to three hemophilic patients; blood coagulation in one case was repeatedly kept normal for some days. The coagulation defect responsible for hemophilia concerns plasma rather than platelets, according to Patek and Stetson (1936) and Patek and Taylor (1936), who isolated from human plasma a clot-accelerating "globulin substance" "closely similar" to that of Bendien and Crevald; its physicochemical properties were studied further.<sup>526, 549</sup> The substance, injected intramuscularly, markedly reduced coagulation time of hemophiliacs. The first and successful use of maggot therapy for infected wounds of hemophiliacs was reported.<sup>548</sup>

### ALLERGIC ARTHRITIS

Little appeared to clarify the term "allergic arthritis" but several writers manifested their receptivity to the idea that offending food or bacterial antigens can produce allergic arthritis in susceptible persons. Ishmael and McBride "found such foods as grapefruit, prunes and coffee to be offending

antigens. As a rule the increased pain, swelling and redness comes on one and one-half to two hours following the ingestion of the food and lasts for about three days. The leukopenic index and intradermal skin tests are used as the laboratory test for sensitivity." Cmunt supported the idea that allergy forms the common basis of several of the rheumatic diseases. He observed a "typical case of allergic arthritis in a patient whose knee was swollen after eating sauerkraut, fruit, buttermilk and yohimbine." To Cmunt gout is also an allergic reaction in persons sensitive to certain foods, not necessarily purines; mentioned was a case of acute gouty arthritis precipitated by milk, but not by ham; another precipitated by gherkins.

[No details concerning these cases were given.—Ed.]

Service saw four patients, each with a family or personal history of nonarticular allergic manifestations who developed idiosyncrasies to food or digestive difficulty and later developed intermittent "hydroarthrosis of allergic origin," relieved by avoidance of offending food antigens.

1. A woman, 34 years old, began at the age of 30 to have, at irregular intervals, pain and stiffness of a shoulder lasting severely three to five days, mildly seven to 10 days more. Association with ingestion of chocolate finally was noticed. Eosinophilia, 6 per cent, was present. [Eosinophilia as high as 15 per cent occasionally accompanies atrophic arthritis.—Ed.] "Food tested," she reacted (skin?) to several foods including chocolate. Avoiding these foods she was free of gastrointestinal symptoms and shoulder pain; eating them she experienced gastric disturbances and "hydrarthrosis," once with special severity within 24 hours after eating large amounts of milk and chocolate. Leukocytes fell from 6800 to 4050. Roentgenograms showed no arthritis.

2. A man, aged 46 years, had "gastrointestinal allergy" for seven years, asthma three years. During severe asthmatic paroxysms he developed tenosynovitis and hydrarthrosis of hands and fingers which persisted a week or more after the asthma subsided. Avoiding foods and epidermals to which he was sensitive he escaped asthma and hydrarthrosis.

3. A woman aged 59 years had hay fever, "gastrointestinal allergy," chronic hypertrophic arthritis of the cervical and thoracic spine and "arthritic changes" of the shoulders and right knee. Avoiding 22 foods to which she was sensitive she noted relief of symptoms in shoulders and neck. Eating citrus fruit caused "an immediate return" of symptoms therein. "Because of the marked limitation of motion as well as pain, a hydrarthrosis was considered to exist in the shoulder region." [Criteria for such a diagnosis were inadequate.—Ed.]

4. A woman aged 58 years with "gastrointestinal allergy" for three years, had hives for three months; shortly thereafter she noted stiff swollen fingers, later painful stiff shoulders. Food tests were negative. Eliminating wheat, beans and potatoes, she was free of pain and swelling in hands and shoulder. The hives persisted "until splenic fluid was given." One of the foods produced definite leukopenia.

[There seems to be no good reason to deny the possibility that in certain cases articular tissues, like so many others, might well react to offending food antigens. Yearly we have briefly described the cases of so-called allergic arthritis to get a more definite picture of the supposed entity but to date no clear syndrome has emerged. No consistent clinical picture has been described; practically no pathologic data have been offered. Case records have been notable for the absence of important details; diagnoses have been based on meager clinical evidence incriminating certain foods, on

skin tests and leukopenic indexes which are generally regarded as of doubtful significance and, most important, on supposedly positive therapeutic tests. The latter would be much more significant were it not that spontaneous remissions are so common in all arthritides. Current reports do little to clarify the syndrome; the cases noted above were certainly not of true intermittent hydrarthrosis. Those who recognize "allergic arthritis" from foods may have the right idea but they are urged to present more comprehensive studies on the clinical and pathologic aspects of the supposed entity and particularly to make more rigorous and prolonged observations on therapeutic and provocative tests.—Ed.]

### METABOLIC ARTHRITIS

Incapable of accurate definition, this term was avoided almost completely in the year's literature. We would agree with the remark: "Metabolic disturbances as a cause of rheumatism are in a very uncertain position."<sup>552</sup> As noted in previous Reviews those who advocate the use of sulfur for atrophic and hypertrophic arthritis consider these diseases due to a disturbance in sulfur metabolism, hence examples of "metabolic arthritis." A supposed example of "metabolic arthritis" was reported by Engel: the case of a child first seen at the age of three years suffering from recurrent arthritis of a hip and acetonemic, cyclic vomiting. Four spells of coxitis were separated by normal intervals of several months; each coxitic spell ended in the course of a severe attack of acetonemic vomiting, which suggested to Engel that the acetonemia was not caused by the arthritis but was a primary feature. The patient had no attacks in 14 years. Seen again at the end of that time, the head of one femur was thickened and the neck shortened. The question was raised whether toxic substances (acetone, aceto-acetic acid, etc.), prevalent in recurring vomiting, may have had an elective affinity for articular cartilage similar to that of homogentisic acid in ochronosis (alkaptonuria).

[The significance of this interesting case is difficult to interpret. One cannot be certain which preceded—the coxitis or the acetonemia.—Ed.]

### ENDOCRINE ARTHRITIS

*Menopause Arthritis.* Endocrine, climacteric or menopause arthritis occasionally was mentioned in the usual vague manner. Some considered menopause arthritis synonymous with hypertrophic arthritis; others considered it a separate disease, with distinctive features in its early stage but later indistinguishable from hypertrophic arthritis. Without committing himself to details, McConkey considered abnormal endocrine function, especially of adrenals and thyroid, a fundamental factor in the causation of chronic, especially hypertrophic, arthritis. According to White "climacteric arthritis" results from endocrine changes occurring in women at the menopause, resembles hypothyroidism in its early stages and is indistinguishable from osteo-arthritis in its later stages. Without clinical definition, Hartfall, Garland and Goldie noted the effects of chrysotherapy in 23 pa-

tients with "chronic villous arthritis (climacteric or menopausal)" aged 40 to 66 years with erythrocyte sedimentation rates more than 10 mm. (1 hour) in only seven cases; improvement was marked in seven, moderate in seven, insignificant in nine cases.

Symptoms and treatment of "menopause arthritis" were reviewed by Holmes, who defined it as an arthritis occurring only in women and "commencing within the five or six years preceding or following cessation of menstruation." About the age of 50 years, patients noted insidious onset of aching stiffness, especially of knees and fingers. Affected persons were well nourished, slightly obese, not toxemic. They experienced discomfort when descending stairs, walking, or rising from chairs. Aside from joints, physical signs were "mainly those of thyroid deficiency (although it was stated that low metabolic rates were uncommon) ranging from small localized patches of indurated fibrous tissue to well-defined myxedema." Knees in the early stage are characterized by chronic synovitis: tenderness, thick synovial membrane, crunching sensations, little or no hydrops, no muscle atrophy. Roentgenograms then are negative. Later "the disease closely resembles osteo-arthritis, from which if left untreated it is almost indistinguishable." In hands carpometacarpal and terminal phalangeal joints are generally affected, occasionally wrists. Tender periarticular infiltrations affect the terminal joints; later they ossify as Heberden's nodes. Original studies on articular pathology were not mentioned but the writer's colleague, Franklin, about 1912, did "limited synovectomy" in six or seven <sup>at</sup> such cases and noted "villous synovitis": "The villi were just hyperemic, <sup>st</sup> edematous synovial membrane"; in no case was there any bony change; <sup>f</sup> when the latter occurred it "indicated a change of the pathology—osteo-arthritis supervening on an old menopausal joint."

[Surely this describes nothing more nor less than "the pre-roentgenographic phase" of hypertrophic arthritis. There seems to be no evidence offered to justify recognition of menopausal arthritis as a separate entity. It is to be regretted that current writers on "menopausal arthritis" can either present no data on its pathologic reactions or must rely on a brief study 25 years old, rather than presenting studies based on the newer knowledge of articular pathology. The latter might quickly settle the issue.—Ed.]

Early and appropriate treatment will bring about complete cure in the majority of cases, or at least will arrest the disease before crippling ensues, according to Holmes, who prescribed removal of obvious septic foci, correction of constipation, a diet low in carbohydrates and calories but rich in vitamins, reduction of trauma, moderate exercise, analgesics, iodine, thyroid at times, physical therapy and estrogenic hormone, 1000 to 10,000 international units injected every other day.

[Estrogenic hormone, at current prices, would cost \$0.50 to \$1.50 a daily dose, a price prohibitive to most patients even were the substance of assured value for joints. In some preparations 1 rat unit equals approximately 5 international units.—Ed.]

According to Miller, "menopause arthritis would be best described as osteoarthritis from the trauma of obesity occurring at the menopause." In conclusion we would agree with O'Reilly: "At a time when aging bacteriology is being deserted for the fresher promises of the endocrines, an undue significance may be paid to [endocrine arthritis.] It is well to note that there is little evidence of endocrine disturbance in [patients with hypertrophic arthritis,] nor in the acknowledged endocrine disorders is there any constant association with arthritis."

*Arthritis and the Parathyroids.* Ankylosing arthritis is no longer considered a manifestation of hyperparathyroidism. To date there have been reported at least 145 proved cases of the latter. All were reviewed by Jacobs and Bisgard: in many cases the skeletal symptoms—backache, leg pains, etc.—had been called "rheumatism" or "arthritis," but no proved case was accompanied by ankylosing arthritis. Furthermore no cases of ankylosing arthritis exhibit the chemical features distinctive of proved hyperparathyroidism. To avoid diagnostic errors, physicians should be familiar with the classical features of clinical and experimental hyperparathyroidism. They have been discussed in previous Reviews: several excellent new reports may be consulted.<sup>11, 12, 97, 117, 118, 227, 339, 343, 680</sup>

#### MISCELLANEOUS TYPES OF JOINT DISEASE

*Intermittent Hydrarthrosis.* In 1929, Weissman-Netter proposed the use of ergotamine tartrate for this condition. By this method Cook apparently stopped the disease in one case.

In 1932 a man, aged 43 years, had had attacks in a knee for 15 years every 21 days (attack five to six days; free interval 15 to 16 days). One tablet of ergotamine tartrate (gynergen, 1 mg.) was given daily for two weeks; then a mild attack lasted two days; one tablet was taken daily for seven weeks with no attacks. Treatment was omitted for one month; an attack ensued. One tablet was given every other day for two months; no attack occurred. Treatment was again stopped for two months; one attack occurred. Gynergen was taken daily for one month; then every other day for six weeks; there was no attack. Between November 1933 and November 1934 one tablet was taken twice a week except for two periods of six weeks each; only during these periods were there (two mild) attacks. Since November 1934 no medicine was taken and attacks have not recurred.

The cause of several recent cases of intermittent hydrarthrosis has been found to be undulant fever.<sup>4, 40</sup> [In our experience most cases of irregularly recurring "intermittent hydrarthrosis" eventually prove to be cases of atrophic arthritis. —Ed.]

*Suppurative Tenosynovitis.* Grennell summarized data on 125 cases in which hands were affected: 67 of the "primary type" (infection implanted directly into the sheath by injury; generally puncture wounds); 58 of the "secondary type" (sheath involved by extension of adjacent infection); none were hematogenous. Flexor finger creases and distal closed spaces were most often affected. Results of surgical drainage were poor; complete or nearly complete function was restored in only 17 per cent of cases. Gross

tendon necrosis occurred in 52 per cent. Recovered at operation were hemolytic streptococci in 36 per cent, staphylococci in 31 per cent (patients so infected responded best); mixed organisms in others (these did poorly). Suppurative arthritis, especially of a distal phalangeal joint, and osteomyelitis were frequent complications. Delays in operation due to errors in diagnosis were frequent and an important factor in the poor results.

[This frank appraisal of the difficulties encountered is commendable.—Ed.]

*Peritendonitis Crepitans; Crepitating Tenosynovitis.* Howard studied 32 cases of this disease, a traumatic tenosynovitis from acute accidental or chronic occupational trauma. Aching, soreness, local warmth, swelling, redness, often edema affect a particular muscle group in arm or leg. One can feel, and with a stethoscope hear, a distinct and often loud, crackling crepitus. Parts affected are tendons generally at or near the musculo-tendinous junction, "never in that part of the tendon supplied with a synovial sheath." Radiocarpal extensions are most often involved. Interstitial deposits of masses and clumps of fibrin produce the crepitation. The pathologic changes in three cases were described. Heat, massage and exercises are usually advocated but merely prolong disability; rest and complete immobilization for a few days are required.

*Synovioma.* Synoviomias are benign or malignant. The latter are rare and of rather recent identity (described by Langenbeck, 1865, named by Smith, 1927). Coley and Pierson reviewed the 20 cases in the literature and added 15 more seen by them since 1900. Synoviomias arise from synovial membrane within joints, from bursae or from pouches or prolongations of joints and may involve connective tissue, tendon sheaths and lymphatic structures. They produce symptoms simulating those of the common articular diseases. After excision they tend to recur and often metastasize to lungs. Joint function is often little impaired. Bone is generally unaffected; hence roentgenograms may be negative unless attention is paid to soft tissue detail. As there may be no palpable tumor, diagnosis often is difficult; it usually is made on exploration, generally of a knee, sometimes of a finger, ankle, metatarsus, hip, elbow or shoulder. Adenopathy rarely occurs. Conservative treatment is inadequate. The tumors are "radio-resistant." Statistics on end results indicate that previous treatments generally have been too conservative. Of the total 35 patients, none survived more than 10 years; six have lived five years; 13 have lived three years; many died within two to five years. Amputation was recommended unless wide excision is still practicable.

*Chondromatosis.* True chondromatosis is rare; most cases so called are examples of hypertrophic arthritis. Only three proved cases were found in the rich material of the orthopedic department of the State University of Iowa. Freund reported them: one in which a shoulder was affected; two, a hip. In one case locking of a hip occurred; the femoral head had been forced almost out of the acetabulum, yet roentgenograms were negative. At

operation, 395 free joint bodies were found. Chondromatosis does not represent a blastomatous change of synovial membrane, according to Freund, but a metaplastic hyperplasia of connective tissue similar to that of myositis ossificans. Supporting this idea is the close embryonal relation of synovia to cartilage (which explains the prevalence of cartilaginous tissue in the disease), and the occasional spontaneous resorption of calcified bodies.

*Ganglia and Synovial Cysts.* Whether ganglia and synovial cysts are slightly different modifications of the same condition never has been determined; clinical distinction between them is often impossible. According to Jensen, their morphology and pathology are essentially the same and they are similar to bursal hygromas. [One of us, J. A. K., does not agree.—Ed.] However, the latter differ from the former in that they have useful function; in ganglia and synovial cysts the bursal functional aim is absent. Theories on the origin of ganglia and synovial cysts were reviewed. Jensen concluded that they originate from embryologic arrests in the process of the development of periarticular tissues and synovial membranes, and have little or no relation to trauma. Jensen presented clinical and pathologic data on 21 simple cystomas (generally affecting wrists, occasionally fingers; essentially symptomless) and 23 cysts with pain and some limitation of motion. A few of the latter were tuberculous. From their study of 50 cases of ganglion, De Orsay, Mecray and Ferguson concluded that trauma is a definite etiologic agent and that the masses arise from degenerations of mesoblastic tissue. They appear first as solid masses; small cysts later form and coalesce as large cysts by disappearance of intercystic septa. Contents were believed to be myxoid, not mucinous; hence the process is one of degeneration of collagen fibers rather than a secretion of connective tissue cells.

Treatment by sclerosing solutions effects cures occasionally. Permanent cures can be expected in about 50 per cent of cases by simple rupture and dispersion; in about 85 per cent by excision. Recurrences result from continuation of the degenerative process in tissues adjacent to the original ganglion<sup>187</sup>; hence all tissue undergoing myxoid degeneration should be removed by fairly wide excision of tissue.

*Hypertrophic Pulmonary Osteo-Arthropathy.* Three reports on this condition appeared; theories on etiology and pathogenesis were reviewed but no new data thereon were offered. Pulmonary neoplasms were the basis of Craig's four cases: three were at first called "rheumatoid arthritis"; one, "acromegaly." Causes in Cushing's five cases of clubbed fingers and osteoarthropathy were lung abscess, empyema, bronchiectasis, congenital heart disease, biliary cirrhosis. Kennedy noted a case in which the patient was a boy, seven and one-half months old—the youngest patient so far encountered. At the age of three weeks a series of infections began, including multiple lung abscesses with enlarged liver and spleen at five months. Death occurred six weeks after rib resection; detailed necropsy data were given.

*Scleroderma.* Periarticular tissues of fingers and toes are frequently affected in scleroderma; patients so affected often complain of "rheuma-

tism," phalanges being puffy, stiff, sometimes painful. Calcium metabolism in scleroderma was studied by Cornbleet and Struck, who could find no evidence of parathyroid dysfunction but noted retention of calcium and phosphorus in the body, excretion of only small amounts in urine. Large daily doses (200,000 to 300,000 international units) of vitamin D seemed of benefit; this increased urinary calcium and provoked a loss of calcium and phosphorus from the body. Eleven patients were treated: at least four months of treatment were required for improvement. An hypothesis was offered: Scleroderma is initially due to a toxin which injures the collagen syncytium; these injured tissues secondarily take up calcium, thus accounting for the frequently observed positive balance in the disease. Massive doses of vitamin D produce a negative balance, apparently at the expense of calcium deposited in collagen and muscle. [Were this theory correct would not the use of parathormone be more effective and perhaps safer? However, it is difficult with any decalcifying agent to remove calcium and phosphorus from soft tissues.—Ed.]

*Malignant Lymphoma with Articular Symptoms.* Rheumatic types of pain may be the only early symptoms of the leukemias with lymphomas; Floyd noted six such cases among children. They complained of pain in various joints often long before changes in blood or lymph nodes were noted. Diagnoses made by biopsy were as follows: malignant lymphoma in one case, lymphatic leukemia in two, myelogenous leukemia in two, Hodgkin's disease in one. Severe anemia, much more profound than that in atrophic arthritis, was present in all.

*Calcium Deposits about Joints.* Calcium deposits "exactly similar" to those frequently present about the shoulder (in supraspinatus muscle, articular capsule, or subdeltoid bursa) were found by Hitchcock about various joints—hip, knee, ankle, elbow, wrist, metacarpal and phalangeal. They may be symptomless or associated with acute or chronic inflammation, at times severe pain, redness, swelling, fever. Reports of nine cases were given. Occasionally trauma was an obvious cause; in other cases a history of trauma was absent. There was no evidence of metabolic derangement or infection; cultures of tissues and animal inoculations gave negative results. Hitchcock advised surgical evacuation of the deposits. On incision, a greasy, mortar-like calcium paste was found in a tense sac with inflamed tissues about it, and within the sac necrotic tendon or connective tissue. Postoperative convalescence usually was uneventful. If incision is not made, the inflammatory hyperemia may be sufficient to cause absorption of the calcium and lead to self-cure, but this may take several painful weeks. Diathermy treatments seemed to promote absorption and healing in some cases.

De Lorimier studied effects of roentgenotherapy on 31 cases of "pararthritis" with 48 calcareous deposits in the following tendons: supraspinatus 20 times, infraspinatus 11, teres minor three, triceps brachii one, pyramidalis six, gluteus medius one, obturator internus three, adductor



magnus one, flexor digitorum one, flexor hallucis one. Calcareous deposits about a shoulder were generally not in the subacromial bursa but in any one of several tendons: supraspinatus, infraspinatus, teres minor, triceps brachii. Some deposits were painless and found accidentally; others were associated with symptoms of acute or chronic "para-arthritis." Results of roentgenotherapy follow: Symptomless calcareous deposits were not absorbed; in cases in which symptoms were mild or moderate, there was complete or marked calcareous absorption and relief of pain; in cases with very acute pain, results were best—marked relief of pain and rapid absorption of deposits. Since irradiation had no effect on symptomless deposits, obviously results are not affected by irradiation alone; irradiation probably initiates an inflammatory reaction which somehow contributes to the "absorption potential" and affords most effective relief of pain.

[When seen surgically these deposits are described as "mortar-like," "creamy," or "tooth-paste-like" deposits of calcium; they are not bone. As will be noted under comments on subacromial bursitis, when marked hyperemia is present deposits may rapidly disappear spontaneously. Simple immobilization of a shoulder for 24 hours may markedly relieve pain and muscle spasm in acute cases. How effective or superior roentgenotherapy really is remains for further studies to determine. It would have been of interest had De Lorimier treated a control series otherwise than by roentgenotherapy—by measures hereinafter noted.—Ed.]

*Ehlers-Danlos Syndrome.* Features of this syndrome include: (1) hyperelasticity of skin; (2) friability of skin and its blood vessels, resulting in formation of papyraceous scars, e.g. about knees; (3) "looseness" or hyperextensibility of joints, particularly of fingers and thumbs. In some cases cystic, subcutaneous nodules are present. Three cases with striking familial features were noted by Stuart; seven cases by Weber. The syndrome may represent a congenital developmental mesenchymal dysplasia.

[Joints were apparently symptomless.—Ed.]

*Juxta-articular Adiposis Dolorosa.* Obese multiparas past middle age are prone to have painful masses of fat near joints, especially over the medial aspects of knees and elbows and lateral aspects of ankles and hips. Kling carefully analyzed many aspects of this syndrome as seen in 125 cases. It almost never affects males. In women it occurs at the time of the menopause. Blood counts were normal; sedimentation rates were normal in a third, moderately elevated in the rest. In a third the basal metabolism was slightly subnormal. Blood calcium was normal; blood cholesterol of 14 of 16 patients examined was increased. Symptoms included pain, weakness, stiffness, coldness and paresthesia of extremities. Pathologic reactions in biopsied tissues were minimal. The condition was often associated, causally according to Kling, with hypertrophic arthritis. Various treatments were valueless. The condition may represent the early stages of true Dercum's disease. Other theories were discussed.

[This is a thorough study of a subject about which little is known.—Ed.]

## DISEASES OF MUSCLES AND FIBROUS TISSUES

*Rupture of Muscles and Related Tissues.* Ruptures of muscles and tendons are common injuries but are often misdiagnosed and treated for arthritis, bursitis or sprain. Ruptures most frequently afflict physically active middle-aged persons whose age has reduced their tolerance for stress and strain. Conwell and Alldredge listed the factors which predispose to rupture: senility, various diseases (arthritis, myositis, acute infectious disease, arteriosclerosis, syphilis, tuberculosis, neoplasm), physiologic predisposition, occupation and fatigue. Disease definitely is a predisposing factor but is not necessary. Ruptures may affect many muscles, most commonly those of the calf, extensors of the leg, biceps, Achilles tendon, extensor of the thumb; less frequently supraspinatus, rectus abdominis, extensors of the fingers, adductors of the thigh and triceps. Signs and symptoms peculiar to rupture in these various regions were illustrated in case reports by Conwell and Alldredge and by Compere and Siegling; the latter in particular discussed traumatic affections of the extensor apparatus of the knees. Examination should be made for localized pain, loss of function or painful function of a muscle or, particularly, a defect or hollow in a muscle or tendon. Roentgenograms of soft tissues may be helpful in diagnosis. Early diagnosis and treatment may prevent prolonged disability. Individualized treatment is necessary: Complete ruptures generally should be sutured; partial ruptures may heal during immobilization.

*Classification of Diseases of Muscles.* Omitting traumatic lesions, Slocumb classified muscle diseases thus:

- I. Parenchymatous myositis
  - A. Suppurative myositis
    - 1. Primary suppurative myositis
    - 2. Secondary suppurative myositis
  - B. Nonsuppurative myositis
    - 1. Dermatomyositis
    - 2. Primary myositis fibrosa
    - 3. Trichinous myositis
- II. Myopathies (primary diseases of muscles, secondary changes in the somatic nervous system)
- III. Interstitial myositis
  - A. Myositis ossificans
    - 1. Progressiva
    - 2. Traumatica
    - 3. Circumscripta
  - B. Intramuscular fibrositis ("muscular rheumatism")
    - 1. Primary intramuscular fibrositis (muscular rheumatism, lumbago, torticollis), a disease unaccompanied by, and independent of, any other recognized disease

2. Secondary intramuscular fibrositis (involvement of muscles and fibrous tissue in various diseases: rheumatic fever, gonorrhea, gout, influenza, etc.)

Commonest of all these diseases is muscular rheumatism, acute or chronic, unaccompanied by other diseases. Because pathologically muscular rheumatism is accompanied by no significant parenchymatous lesion, no true myositis or affection of muscle cells, but at times reveals minor, but none the less significant, lesions in interstitial tissue of muscles, many consider the term "fibrositis" more correct than "myositis." True myositis actually is rare.

### FIBROSITIS

The different anatomic forms of fibrositis, symptoms peculiar to each form, their supposed etiology and their treatment were again discussed by several writers.<sup>22, 84, 88, 121, 147, 240, 263, 264, 338, 395, 627, 683, 720</sup> Reviews of the subject were made by Buckley, Fletcher, Krusen and Slocumb. Fibrositis is of course not confined to intramuscular fibrous tissue but can involve fibrous tissue anywhere.

*Primary Fibrositis (Intramuscular; Periarticular).* Clinical characteristics of the acute and chronic phases of intramuscular and periarticular fibrositis were described.<sup>22, 88, 147, 240, 264, 338, 627, 683</sup> According to some, physicians too often mistake periarticular fibrositis for atrophic arthritis or for psychalgia affecting joints; patients are either overtreated and given the prognosis of arthritis, or they are undertreated and handled as neurotics. The incidence of periarticular fibrositis is not widely appreciated. During two years Traeger recorded 900 admissions to the arthritis clinic of the Hospital for Ruptured and Crippled, New York City. Among them were 262 patients with stiff, painful, aching joints (not confined to weight bearing regions), worse after rest, better after exercise; most of them were referred as "arthritics"; 128 had symptoms less than two years, 134 had symptoms two to 18 years, yet in none of them were discovered any objective, including roentgenographic or laboratory (for instance, sedimentation rates) abnormalities. Obviously they were not cases of atrophic or hypertrophic arthritis. For reasons given the diagnosis of periarticular fibrositis was made.

*Pathology.* No new data on pathology were reported. As always, most writers quoted Stockman's findings (1920) rather than their own. The common understanding was that the acute stage consists of edema of low grade with serofibrinous exudate, a slight nonpolymorphonuclear cellular reaction; features of the chronic stage are new fibrous tissue lying in an amorphous serofibrinous matrix, few fibroblasts, no leukocytic reaction, thickening in and around small blood vessels, and the formation of tender fibrous indurations or nodules of varying sizes and shapes.<sup>22, 147, 240, 264</sup> [Two of us, W. B. and M. H. D., cannot accept this description of so-called fibrositic nodules and doubt their existence. Should such exist it is difficult to believe that

simple massage could make them disappear.—Ed.] In Fletcher's experience the structure of the nodule is not typical and apparently consists of "fibrous tissue showing evidences of inflammation and degeneration." Traeger found nodules in a minor percentage of cases. Others<sup>204</sup> insist they are practically always present, their discovery being a matter of "patience and practice." According to some (Clayton and Livingstone): "It often takes five minutes of careful kneading to localize the tender nodules and, unless these are accurately localized treatment cannot be efficient. The average practitioner would never pronounce lungs normal without an examination of at least three minutes, yet few will spend the same time in examining for fibrositis." With increasing experience Krusen found nodules with great frequency: "They are not easy for the novice to find"; 50 per cent of the nodules in Krusen's cases were painless.

*Etiology.* Previous ideas were restated. Precipitating factors in Traeger's cases were chills, fatigue, trauma, chronic strain, nervous exhaustion, influenza, respiratory and other infections. The usual hypotheses on causation were entertained: The disease probably represents a tissue reaction to bacterial or metabolic (chemical) toxins.<sup>88, 147, 204</sup> Buckley and Gordon considered metabolic toxins the more likely cause. According to Gordon two chief factors operate: mild hypothyroidism and an imbalance in the autonomic system, with consequent inefficiency of circulation and elimination. These lead to accumulations of metabolites in the least vascular tissues of the body; i.e., fibrous tissue.

[These are but speculations; the cause or causes of the disease are unknown. No studies on metabolic rates were currently noted; no conclusive evidence has ever been given to prove that hypothyroidism is a consistent or even a frequent feature of fibrositis, or that body tissues or fluids contain excesses of the known metabolites.—Ed.]

*Treatment.* Again no new data were given. The usual measures were advocated: in acute cases, rest in bed, a saline purge, acetylsalicylic acid (15 grains every four hours,<sup>240</sup> heat, counter irritants (dry cupping, acupuncture<sup>121</sup>), carefully selected physical therapy, sometimes injections of procaine. Treatment of chronic fibrositis included rest from irritating trauma, removal of foci, a trial of typhoid vaccine or desensitization with some streptococcal vaccine, physical therapy, above all eradication of painful fibrous indurations by firm massage. "Discover the nodule and rub it away" was the universal admonition.<sup>204</sup> Many warned that "this is a painful business."<sup>140, 240, 204</sup> The treatment is "painful and unfortunately not likely to be of much value unless it is" (Fletcher). "Massage must be deep and will therefore be painful"; the fibrous nodules must be "thoroughly broken up" (Copeman). Although painful, treatment must be kept up progressively, effective treatment is somewhat exhausting and only a few nodules should be treated at a time.<sup>240</sup> In some cases, massage should be given only two or three times a week because one may be "stirring up toxins"<sup>720</sup>; heat can be applied daily. Most patients obtain some relief

from heat but some are not "heat-lovers"; they cannot stand heat in any form as it aggravates their pain.<sup>664</sup> General principles and methods of physical therapy for the disease, especially the nodules, were described.<sup>88, 264, 395</sup> Painless nodules should be left alone. Admitting that he was able to relieve many patients by the physical methods described and that massage often causes disappearance of the nodules, pain, tenderness and stiffness, Krusen nevertheless added: "One is still led to wonder whether these nodules are as important as many writers believe and whether they can be 'rubbed away' as consistently as some state."

Vaccines and removal of foci were generally disappointing to Gordon who, on the basis of his concept of the disease, recommended thyroid extract, atropine, ephedrine and hyoscine. No relief should be expected from sulfanilamide.<sup>714</sup> Gold is useless and may be harmful.<sup>147</sup> Skin should be subjected to a "hardening process"—ultraviolet ray therapy and friction baths.<sup>22</sup> [In chronic cases treatment in our experience is often disappointing.—Ed.]

"*Senescent Fibrositis.*" According to Gordon<sup>84</sup> and others fibrositis accompanies every case of osteo-arthritis; indeed the patient's discomfort is often due to the fibrositis more than to the arthritis. Previously this form of fibrositis usually has not been separated from "primary fibrositis" but current writers are speaking more of "senile," "senescent" or "degenerative" fibrositis.<sup>84, 147, 683</sup> Copeman regarded senile fibrositis worthy of separate identity for it is much more resistant to treatment than is ordinary fibrositis. Buckley<sup>84</sup> spoke of "degenerative fibrositis." "Nodule formation is not conspicuous in the fibrositis of this degenerative type, which is more generalized. The process tends to become a fibrosis, a characteristic of senescence." According to Buckley, "The fibrositis of advancing years is due to the action of metabolic toxins such as uric acid, and other products of disordered metabolism and tissue breakdown, and not to bacterial products as a rule. Accumulation of lactic acid, the product of muscular activity, may also act as an irritant." Again, it was Buckley's<sup>86</sup> opinion that gout, or at least hyperuricemia (uric acid more than 3.7 mg. in men; more than 3.5 mg. in females) is frequently associated with attacks of fibrositis which may be chronic in onset and course and not acute, as are the ordinary features of the disease. Indeed, he regarded gouty fibrositis more common than gouty arthritis.

[Few American physicians agree with this concept or would consider chronic fibrositis a manifestation of gout. If gout were found to be the basis of any case of fibrositis that case should be labelled, not "primary" fibrositis, but "gouty" fibrositis.—Ed.]

*Comment.* [Too many physicians welcome the term "fibrositis" as a convenient scrapbasket into which to discard cases of varied vague aches and pains. Those who erroneously consider intramuscular fibrositis as equivalent to myalgia, and periarticular fibrositis as synonymous with arthralgia, will adulterate their groups of fibrositis with cases of joint and muscle pains due to postural strain, thyroid deficiency, menopause, fatigue, etc. Such physicians make the diagnosis of fibrositis much too often. Other physicians, seeing the term used as a catch-all,

refuse to accept the entity and never make such a diagnosis. In the present state of knowledge no one can say how right or how wrong either group is but they are probably both wrong.

Although of necessity current comments on etiology and pathology of fibrositis are vague, several of the reports noted include clear clinical descriptions of primary fibrositis and its differentiation from the "algias." Physicians would do well to read them sympathetically because in every country there are huge armies of persons who might be said to be "rheumatic" (in the common sense, not in that of rheumatic fever), but not "arthritic," who ache and get stiff but don't swell or get deformed, of persons whose skeletal system is constantly at the mercy of barometric change, shifting winds and air-conditioning. Symptoms are not confined to joints under postural or occupational strain. Although their disease may make them irritable and nervous, they are not true or primary neurotics. Assuredly they are not arthritics, not even "early arthritics," because long observation reveals the persistent absence of objective, roentgenographic or chemical abnormalities (except nodules if and when discovered). Although the term "fibrositis" may seem vague to some and the syndrome it implies incompletely understood, application of this term (or one more suitable) to the cases described herein seems in order. To file these cases away to be forgotten without even a tentative designation is to bury one's head in the sand, and will not help to settle the issue. But to adulterate the syndrome with an array of "algias" will help to perpetuate confusion. What is needed most of all is a comprehensive clinical and pathologic study of the various types of fibrositis. Assuredly the chronic, secondary fibrositis of atrophic arthritis with its muscle atrophy, the acute secondary fibrositis of rheumatic fever, the "fibrositis of gout" (if there is such a disease) should be expected on careful study to reveal pathologic reactions distinct from those of primary intramuscular fibrositis in which significant atrophy rarely, if ever, occurs. If there is a difference between ordinary primary fibrositis and senescent fibrositis studies on pathology should be helpful. But as a basis for these studies information should be obtained regarding the progressive intramuscular changes incident to each decade in the lives of persons without muscle symptoms.—Ed.]

#### PHARMACEUTIC MYALGIAS

Bach briefly reminded physicians of "rheumatism from chemotherapy"; expressions of idiosyncrasy from arsenic, bismuth, mercury, gold, barbiturates, chloral, atophan or antipyrin.

#### "PSYCHONEUROTIC RHEUMATISM"

To conscientious physicians harassed by doubt whether to classify a given case as one of fibrositis, myositis, postural fatigue or neurosis is recommended Halliday's "preliminary report" on psychologic factors in rheumatism. It cannot be reviewed adequately here but it is a worthy attempt to explain the pathogenesis of "psychoneurotic rheumatism."

The rôle of psychologic factors in producing pain, tenderness and stiffness in various muscles and joints was discussed. Such symptoms, unassociated with organic changes, often are erroneously labelled "rheumatism," "fibrositis," "neuritis," "sciatica," "lumbago," "myodynia"—labels which are "convenient, comprehensive, scientifically vague." But they are in fact symptoms of a chronic psychoneurotic anxiety state in which the "rheumatism" is but an episode. Representative cases were described. Emotion involves the primitive brain, autonomic nervous system, and endocrine glands. Acting through these structures emotional or psychologic

factors may profoundly affect bodily chemistry, rhythm, secretion and even structure. When a person is grieved by the loss of a beloved person or object, between paroxysms of grief he may actually feel sore and stiff as if he had been thrashed. As time passes these bodily reactions usually subside; sometimes they persist in their original or in a modified form. The acute emotional loss of appetite may merge into chronic anorexia, regurgitation, vomiting; the pain of a "broken heart" may persist as precordial soreness or neurocirculatory disorder; in the locomotor system soreness and stiffness and the heaviness of grief may merge into a fatiguing "rheumatism." Thereafter the victim's attention is no longer focused on his grief but is dominated by the physical expression of grief which he henceforth interprets as evidence of disease.

Halliday outlined methods for recognizing, investigating and differentiating such cases; also he commented on their interpretation. Pain may be an expression of inferiority; occasionally persons develop pain in structures which are physiologically or anatomically deficient. The pains not only rationalize the inferiority to the victim but also afford an excuse not to use the inferior part. Examples were given where pain and stiffness, especially in back or neck muscles, invoked the mechanism of symbolism (e.g., a case of "symbolic lumbago"); such symptoms are called "body language." Analyzed in detail were 21 cases (eight males, 13 females) of "psychoneurotic rheumatism." Some of the patients were anxious or depressed, but others were detached, placid, cheerful and smiling. Indeed the trouble more frequently affected self-respecting, independent persons. Commonest symptoms were fatigue, weakness, general soreness, palpitation, sleeplessness, but especially pain and stiffness; in three cases actual articular swelling was noted. The translation of psychoneurotic emotionalism into "rheumatism" took from a week to two years after the emotional encounter. Regions affected were neck only in four cases, neck and left arm in seven, left arm alone in six, right arm alone in one case. Halliday stressed the frequent localization in the extreme left aspect of the body, top of the left shoulder and outer aspect of left arm. The 21 records were epitomized: "I experienced misfortune, I took it ill, I felt it sore and stiff."

In Scotland 10 to 12 per cent of all persons incapacitated for work are labelled "rheumatic." In two series of such cases Halliday found that 39 per cent (of 145 "rheumatic" cases) and 37 per cent (of 62 cases) were pure examples of psychoneurotic rheumatism. Most of these patients are treated by physical means to rub away their pain and stiffness. This treatment usually is contraindicated as it only serves to fix the disease more firmly. These patients must be handled in a special way. They "love" a variety of treatments; they may improve temporarily under sympathetic hospital care but they continue to be ill because of the future more than the past. "Many patients are not prepared to take the consequences of becoming well."

#### EPIDEMIC MYALGIA OR PLEURODYNIA

Features of two or three epidemics were reported. Symptoms were as outlined in last year's Review.<sup>4</sup> Pickles studied 31 cases among children and young adults in 1933 in England. The characteristic paroxysmal thoracic or abdominal pains, with fever and rapid, shallow respirations, were noted. Patients recovered quickly without sequelae; it was intimated that their main danger was that they might fall into the hands of surgeons and be operated on for acute abdominal disease. The general absence of cough and of vomiting were points suggesting the absence of pneumonia or appendicitis. Further studies on the Cincinnati epidemic of 1935 were reported: 282 patients were affected (Harder 1936); among these were 70 children,

studied by MacDonald, Hewell and Cooper. There was abdominal pain alone in 41, abdominal and thoracic pain in 14, thoracic pain alone in seven, and "indefinite pains" in eight cases. Nausea affected 35 per cent and, contrary to the experience of Pickles, vomiting affected 31 per cent of patients. Abdominal pain was usually generalized or in the upper part; it was in the right lower quadrant in only 10 per cent of cases. Bacteriologic studies were made in 26 cases (Cooper and Keller). Cultures from blood were negative in 23 cases, from spinal fluid in three. Consistently present in nasopharyngeal cultures were green-producing, slightly hemolytic, streptococci. Injected into animals they commonly produced pulmonary lesions, but no definite evidence was obtained that they were the cause of epidemic myalgia.

In true epidemic myalgia, muscles of the chest and abdomen are affected. In an epidemic of some sort of myalgia at Rugby School, England, Smith<sup>63a</sup> noted common involvement of neck muscles, which were very painful and tender, often associated with slight fever and regional adenopathy. In "ordinary stiff neck" the neck is turned toward the affected side; in this type the neck was turned away from the affected side, presumably because diseased muscles were so weak their tone was lost.

*Myositis Ossificans.* Chaudhuri reported a case of progressive myositis ossificans. The patient was a boy two years old. Symptoms were stiff neck and bony protuberances of one year's duration in cervical, scapular, lumbar and sacral regions. Microdactylia was present. Roentgenograms disclosed bony deposits in various muscles. A case of localized post-traumatic myositis ossificans, producing a firm, bony mass on the lateral aspect of a boy's thigh was noted by Hunt. Some consider "rider's bone" an example of traumatic myositis ossificans. Moore reported a case in which a stalactite-like tumor at the origin of the rectus femoris was presumably initiated by riding strains. The etiology of ectopic bone was briefly discussed.

*Relapsing, Febrile, Nodular, Nonsuppurative Panniculitis: Weber (1925)-Christian's (1928) Disease.* This "new" disease is characterized by crops of subcutaneous nodules which occur during febrile periods and which on histopathologic examination are found associated with a peculiar type of fat atrophy. Eight cases have been reported in the literature; to them Bailey's five cases may be added. Symptoms were recurrent attacks of malaise and fever of widely varying degree, accompanied by subcutaneous nodules; predominant incidence was among women; nodules were on the trunk or extremities, mainly on the thighs; there was a tendency to subcutaneous atrophy with its resultant depression at the site of involution. Pathologic reactions were detailed. The disease may represent a special reticulo-endothelial response in which drugs, particularly iodine, may be precipitating factors. It may cause death.



## DISEASES OF BURSAE

It is said that, with the possible exception of subacromial bursae, human beings are not born with bursae; they develop after birth in response to the functional demands of movement (Black, 1934). Superficial bursae (e.g., olecranon, prepatellar, that over the head of the metatarsophalangeal joints of great toes) lie in connective tissue between skin and bony prominences. Deep bursae (e.g., subacromial or subdeltoid and those over the greater trochanter of the femur or over the ischial tuberosity) lie between muscles and moving bony points. The common conditions affecting each were discussed by Kaplan and Ferguson. Chief factors are trauma and infection. [Noninfectious inflammation, as in gout, should be added.—Ed.] As a result of trauma a bursa, previously only a potential space, may fill with serosanguineous fluid and become a palpable, fluctuant sac. With healing, fluid is resorbed but varying amounts of cellular debris and fibrin remain to undergo complete or partial organization. The deep bursae which may be affected are the subacromial (most common), subgluteal, iliopsoas, supratrochanteric, semimembranosus, pretibial. Because of its frequency and special features, subacromial bursitis will be discussed separately.

For acute traumatic bursitis treatment outlined was as follows: immobilization in splints three to four days, by elastic compress bandages longer; cold applications at first, warm ones later; analgesics; aspiration if exudate is marked. For chronic traumatic bursitis the following were recommended: protection from occupational trauma; aspiration and obliteration of sac by sclerosing solutions (details given), or surgical removal if the foregoing fails; heat and aspiration alone are of little value. For suppurative bursitis conservative therapy was advised (splint, hot dressings); later, if the process becomes localized and less acute, incision and drainage. [One of us, J. A. K., advises early drainage.—Ed.]

Wolf discussed bursitis affecting the four bursae of the foot: 1. Those at the dorsum of toes become affected by cramping shoes and pressure of the shoe cap on toes flexed in a claw position. Treatment consists of raising flattened metatarsal arches by foot plates, pads, bandages or rarely by operation. 2. The bursitis at the inner aspect of the bunion joint is usually associated with hallux valgus, less often with osteophytes (hypertrophic arthritis); it is treated by shoe correction, felt or rubber rings and ichthyol ointment. 3. Calcaneal bursitis (without calcaneal spurs) is treated by alcohol dressings, baking, foot support. 4. Achillobursitis is commonly gonorrheal; specific measures or surgical removal were advised.

Moshicowitz noted 20 cases of sartorius bursitis, "an undescribed malady simulating chronic arthritis," affecting obese women, producing pain in both knees, especially on stairs, and resulting from strain of weight bearing. Roentgenograms were negative. Tenderness and occasionally slight swelling were present on the inner aspect of the tibia at the site of the insertion of the conjoined tendon of sartorius, semitendinosus and gracilis tendons. Weight reduction is necessary.

[No surgical proof was given that bursitis, and not tendinitis, arthritis or fibrositis, was present.—Ed.]

*Lesions About the Shoulder Joint (Subacromial Bursa and Supraspinatus Tendon).* The majority of painful shoulders were once considered due to subacromial (subdeltoid) bursitis. The calcification frequently seen about the shoulder was thought to be practically always in this bursa. Some stated later that the calcification rarely was in the bursa, practically always in the supraspinatus tendon. It is becoming more evident that inflammatory lesions with or without deposits of calcium, and deposits of calcium with or without inflammation, may involve any one (or more) of several different periarticular sites. However, because it is at times impossible to differentiate one affection from the other without anatomic dissection, writers continue to use the term "subacromial bursitis" loosely as a sort of collective term for all these lesions; others use the term peri-arthritis or "para-arthritis" of the shoulder to include lesions due variously to true subacromial bursitis, to major or minor ruptures (with or without calcium deposits) of supraspinatus or other tendons at or near the shoulder, to inflammation with calcification but without rupture of these various tendons, and even to calcium deposits about painless shoulders. Greater accuracy in localizing these deposits can be obtained by making roentgenograms with the humerus in extreme internal rotation. By this means islands of calcium which appeared to be in the head of the humerus were shown by Fahey and Harmon to be actually in tendons of the supraspinatus, infraspinatus or teres minor. Deposits in similar locations were noted by De Lorimier.

Five common causes of painful shoulder were described by Ferguson, and Kaplan and Ferguson:

1. Acute traumatic bursitis from direct or indirect trauma: a traumatic inflammation due to contusion of the bursa between the greater tuberosity and acromion, and to slight tears of the supraspinatus tendon. Symptoms include tenderness over the greater tuberosity, and pain on motion, especially abduction. Roentgenograms are negative. Treatment includes immobilization (adhesive strapping or abduction splint), heat, increasing exercises. Recovery is rapid.
2. Acute bursitis with calcification. Patients so affected have intense, constant pain in the shoulder due to inflammatory tension in regions of calcification. There is acute tenderness over the greater tuberosity and motion is impossible because of pain. Roentgenograms reveal large areas of calcification over the lateral edge of the greater tuberosity. Under local anesthesia, tension in the region of calcification should be relieved by incision and evacuation or by aspiration of the deposits; rapid relief of pain and normal function result.
3. Subacute bursitis with calcification. This is a less severe form of the second syndrome. The shoulder can be moved; it is most painful on abduction or when the patient lies on it at night. Symptoms are due to trauma, calcification and reflex spasm of the supraspinatus. Small areas of calcification appear above the greater tuberosity. It is treated by rest, heat, sedatives, injections of 20 to 30 c.c. of 1 per cent procaine into the bursa, exercises; gradual recovery follows.
4. Chronic bursitis causes pain and "clicking" somewhere during abduction; slight stiffness; tenderness over the greater tuberosity. There are defects in the supraspinatus tendon, villi and bands in the bursa, and excrescences, eburnation, and areas of rarefaction in and at the greater tuberosity. Recommended were rest, heat, excision

of villi, bands and excrescences. 5. Tendinitis or obliterative bursitis results from overuse or repeated slight trauma. Adhesive bursitis causes loss of gliding function in the bursa. Abduction and external rotation become difficult. Atrophy and spasm of shoulder muscles may result. Roentgenograms are negative. Recommended were injections of procaine, manipulation, special exercises, physical therapy. Recovery is slow and may be incomplete.

It was admitted that differentiation into such groupings, especially the distinction between simple bursitis and partial tears of the supraspinatus tendon may at times be difficult to make; however, treatment for the two syndromes is essentially similar.

Patterson and Darrach treated 63 patients with "subdeltoid bursitis" by the double needle irrigation technic of Smith-Peterson. Results in the cases were: complete relief in 57, limited motion in two, operation necessary after irrigation in two, no relief in two. In 48 cases the process was acute (under one week); disability after treatment averaged only five days; in eight subacute cases disability after treatment averaged seven days; in seven chronic cases (more than one month) disability after treatment averaged 10 to 14 days, sometimes longer. Deposits of paste-like calcium were sufficient to show in roentgenograms in 48 cases, but results often were good, even when opacities were not seen; hence, irrigation should not be refused those on examination of whom deposits are not found. The assumption that the deposits frequently were in bursae as well as in supraspinatus tendons seemed correct because paste-like calcium was aspirated in the salt solution. In cases wherein deposits were not in bursae but in tendons, relief often was noted even though deposits remained; at other times irrigations were ineffective.

Irrigation seemed indicated in cases in which initial attacks of very acute pain were localized to one spot, not radiating, and in which fuzzy (not dense, round or bonelike) calcium deposits appear to be in bursa, not in tendons. Other patients were treated by physical measures, perhaps aspiration was tried in resistant conditions prior to surgical exploration.

[It is at times difficult to be sure deposits are in bursae; in obliterating bursitis it is difficult or impossible to thrust even one needle into a bursa.—Ed.]

Clayton accepted the view that in subacromial bursitis the lesion is not in the bursa but in, on or under the supraspinatus tendon, and consists of inflammation, necrosis of the tendon, calcium deposits or metamorphosed fat. He did not accept Codman's (1934) view that deposits are due to acute traumatic rupture of some fibers of the supraspinatus tendon. To him the cause was not trauma, hemorrhage or infection but some undefined metabolic disturbance. In severe cases the most pain may not be at the bursa or the site of the deposit but near the insertion of the deltoid; symptoms may be those of brachial neuralgia. Deformities arise not from adhesions, as some believe, but from contractures of muscles and ligaments. In "bursitis" tenderness is limited to a definite area "smaller than a twenty-five cent piece" at the front of the humerus just below the acromion at the

site of the deposit; in chronic arthritis there is tenderness of the entire circumference of the head of the humerus.

Codman is generally recognized as the first to describe rupture of the supraspinatus tendon as a major cause of disability of the shoulders. He has currently written: "As for my own impression that I was the first to call attention to ruptures of the supraspinatus and of the other short rotators, —it has been gently but firmly and permanently removed" by the discovery of a report on the same subject published by Smith, 1834, and reprinted by Codman.

Few surgeons have the opportunity to study the pathology of, and repair ruptures in, supraspinatus tendons within 38 to 72 hours after rupture; Mayer had four such cases, Davis and Sullivan three. Mayer advised certain "important changes" in the technic of surgical repair. Davis and Sullivan also recommended early repair of tendons. Signs necessary for a diagnosis of complete rupture were given and included a history of acute trauma, immediate sharp pain, "a tender point, a sulcus and an eminence at the insertion of the supraspinatus which causes a jog, a wince and soft crepitus as the tuberosity disappears under the acromion when the arm is elevated, and usually also, as it reappears during descent of the arm."

The common disabilities of shoulders are not due simply to acute traumatic rupture of the supraspinatus tendon, according to Skinner, but involve a more widespread disturbance than mere rupture; this is often only an accident in the course of a progressive disturbance involving various structures, but centering around the supraspinatus tendon. Separation of this tendon (which is beneath the floor of the subacromial bursa) from its attachment to the humeral tuberosity has been held to be due to: (1) trauma (rupture and imperfect repair), (2) defects left by calcium deposits, (3) necrosis of tendon or other diffuse pathologic processes, (4) attrition (wear and tear of age). Varied opinions on the mechanism of the deposition of calcium were reviewed. Skinner traced this sequence of events: The anatomic location and function of the supraspinatus muscle are such that it is subjected to stresses which may produce profound changes in the muscle; first is an alteration in the character of its lateral position—from fleshy fibers ending in a short tendon to a wide aponeurosis of fibrous tissue which blends with the infraspinatus. In the muscle weakened thereby other changes ensue: calcification, splitting or rupture of tendon, separation of the sheet from the greater tuberosity, and the establishment of free communication between subacromial bursa and joint cavity. Changes likewise affect the greater tuberosity, intertubercular sulcus and tendon of the long head of the biceps; also, changes take place within the joint. The long head of the biceps is flattened and frayed; the capsular portion of the tendon may disappear. Important factors in the long process of wear on the supraspinatus tendon are the patient's age and occupation. In about 20 per cent of all adult shoulders there are changes in this tendon; in 5 per cent some degree of rupture or splitting will occur.

Among patients benefited by roentgenotherapy, Kahlmeter listed some troubled by acute subdeltoid or subacromial bursitis, "peritendonitis calcarea" and "humeroscapular periarthrititis." For these and other bursae "x-ray therapy is very good." The results of De Lorimier were noted. Results of short wave diathermy given in 99 cases of "subdeltoid bursitis" with calcification, resistant to other measures, were good, according to Feldman; pain was relieved by three to six treatments; function was restored after 10 to 12 treatments. Such therapy presumably produced deep heat, marked hyperemia, muscle relaxation, drainage of exudate, reduction of tension on bursal walls. Calcification may not disappear but its failure to disappear bears no relation to end results. Purulent bursitis is a contraindication to such therapy. Similar therapy was advocated by Humphris.

### MISCELLANEOUS CONDITIONS

*Bone Abscesses Simulating Arthritis.* Three patients with articular pain of five to 14 years' duration, treated as arthritis but due to Brodie's abscesses, were noted by Wagner. Such abscesses begin early in life as epiphysitis, often from avirulent staphylococci. They are chronic, never acute and progress for years, producing bone necrosis, areas of rarefaction and of formation of new bone, partial loss of articular function, occasionally synovitis. Pain is "boring" and is referred to a joint and center of affected bone. Roentgenograms of bones in various positions may be necessary for diagnosis. Surgical treatment gives spectacular relief.

*Lupus Pernio (Boeck's Sarcoid; Osteitis Tuberculosa Multiplex Cystoides).* Features of this disease were excellently reviewed by Longcope and Pierson. This chronic infectious granulomatous condition slowly progresses to involve chiefly skin (eruption, disseminated nodules, large cutaneous nodosities, infiltrations), lymph nodes, lungs ("marbled" or reticulated appearance, diffuse fibrosis) and bones of hands and feet, sometimes other tissues. Fingers may be deformed by subcutaneous nodules symmetrically disposed about interphalangeal joints. In advanced cases there may be relatively painless mutilation, with gradual disappearance of terminal phalanges. Roentgenograms are characteristic: areas of rarefaction and reticulation in medulla of phalanges, sometimes irregular enlargement and distortion of bones but no involvement of periosteum or of joints. Areas of rarefaction often occur as sharply defined, round, punched out spots [and are sometimes mistaken for those of gout, atrophic arthritis or hypertrophic arthritis.—Ed.] Eight new cases were reported; bones were involved in three. The cause is unknown; many consider it a peculiar form of tuberculosis. Data for and against this idea were reviewed.

### OTHER STUDIES

*Experimental Arthritis.* 1. Infectious. Rosenow's strains of arthrotropic streptococci were given intravenously to rabbits by Jarløv and Brinch.

Articular lesions were consistently produced; lesions in other organs occurred much less often; thus Rosenow's theory of elective localization seemed to be supported. The severity of articular lesions varied from pyoarthritis to slowly progressive, symmetrical, chronic, deforming arthritis; in some cases hypertrophic lipping of vertebral bodies occurred. Only by motion picture records and close clinical observations were some of the milder articular lesions noted objectively; they were verified by pathologic studies. Such lesions might well have escaped detection in the work of others.

Joint tissues can be damaged by contact with bacterial toxins alone, not necessarily by whole bacteria. Rigdon made single injections of staphylococcus toxin into knees of rabbits. Reactions included periarticular swelling; exudate of erythrocytes, polymorphonuclear and mononuclear cells; fibrinous synovitis; proliferation of fibrous tissue; focal destruction of cartilage; capsular fibrosis; lesions in adjacent muscles.

2. Traumatic. The articular changes produced in animals by acute trauma (Miltner, Hu, and Fang), and those resulting from the chronic trauma from patellar displacement (Bennett and Bauer), already have been discussed (under "traumatic arthritis" and "hypertrophic arthritis" respectively).

3. Chemical. The changes produced by intra-articular injections into animals of indole, skatole and indole proprionic acid (Forbes and Neale) were noted (under "atrophic arthritis—factor of altered metabolism").

*Articular Roentgenography.* In studying roentgenograms of joints too much attention is paid to bone changes, too little to soft tissues inside and around joints. Roentgenograms made with knees flexed at  $125^{\circ}$  or at  $105^{\circ}$  give better views of intercondylar fossae and may reveal hypertrophic arthritis not visible in ordinary roentgenograms. In Jordan's technic, patients lie on their backs; anteroposterior views are taken of knees flexed at  $125^{\circ}$  and held in this position by a triangular support under the popliteal space. Holmblad found views made by such a technic superior to ordinary roentgenograms but inferior to those taken postero-anteriorly, with patients kneeling with the abdomen supported in a horizontal position, and with the knees flexed at  $75^{\circ}$  (i.e. at  $105^{\circ}$  extension). To study the part played by cortex and cancellous bone in the production of roentgenographic images Lachmann made experimental roentgenographic analyses of bones of cadavers. In arthrograms Hosford demonstrated the complete reestablishment of the synovial cavity of a knee after synovectomy.

*Articular Physiology.* The full report of Bywater's studies on the metabolism of joint tissues appeared; a short summary of it was given in last year's Review.<sup>4</sup> Kling summarized the studies of himself and others on articular physiology. Morphologic and physicochemical studies and experiments show a dual structure and function of synovial tissues. One part is a connective tissue capsule for the binding of articulating bones. Interposed at the intra-articular surfaces are areas for the elaboration of

synovial fluid. The function of normal synovial fluid is lubrication and protection of joint surfaces. Motion is the physiologic stimulus for the production of normal synovial fluid. The function of synovial fluid depends on its mucin content. Mucin is a product of special cell activity and not of degeneration.

*Articular Function.* In an effort to establish norms for a comprehensive investigation of the development of human motor function, Glanville and Kreezer determined the range and velocity of articular motion in normal male human adults. The use of a standard method of grading articular disability in cases of arthritis was proposed by Taylor who set up a table of grades of articular involvement as determined by roentgenographic changes and clinical findings.

[One of us (P. S. H.) long has found it useful to summarize each case thus: for example, "chronic atrophic arthritis, activity grade 2, extension grade 3." This gives a concise picture of a patient with moderately active disease affecting many, but not most, of his joints. The use of some such grading as Taylor's, especially by those who report results of treatment, would be of great value in assisting readers to judge for themselves the worth of any procedure. It is one thing to say, for example, that gold cured such and such a percentage of 100 patients with atrophic arthritis: 50 may have had a mild form of the disease, 30 a moderately severe form and only 20 a severe form. The word "mild" is inadequate, as one patient may have mildly active disease in one or two joints, another may also have the disease mildly active but in a dozen joints.—Ed.]

*Auscultation of Joints.* A survey of the value of auscultation of joints was made by Steindler. In a study of 1600 joints of persons of different ages, Walters (1929) noted grating in only 1.5 per cent of children in the first decade; in 82 per cent of persons in the eighth decade of life. Steindler utilizes a cardiophone and an oscillograph. Sounds emanating from four quadrants of knee joints were studied. Isolated sounds are cracks, clicks or thuds. High pitched cracks indicate hard, dense bodies (e.g. joint mice); low pitched clicks and still lower pitched thuds indicate bodies of greater softness and elasticity (e.g. fringes, semilunar cartilages). Sounds could be localized both as to quadrants and as to position of the joint. Such studies helped to localize loose bodies and injuries to semilunar cartilages. Studies were made on 216 arthritic patients. Results were analyzed in detail.

*Physiology of Muscles.* Lack of knowledge of the chemical changes which take place in muscles and joints and which cause or result from disease is "colossal." The pathogenesis of many of these diseases will not be fully understood without more information thereon. A number of interesting studies on the physiology of muscles under various conditions were reported but can only be referred to here.<sup>37, 59, 154, 214, 216, 300, 307, 436, 592, 610, 635</sup>

*Studies of Pathology.* De Galantha described a method for rapid decalcification of bone by which bone can be prepared for sectioning in as little as three to four days. The method also has the advantage of being

less deleterious to cellular elements of soft parts; hence, better cellular and tissue differentiation with elective staining reaction is possible.

### THE CAMPAIGN AGAINST RHEUMATISM

A few generations ago the hot, swollen, beefy-red joints of gouty patients were so effectively dramatized that it became a matter of distinction to boast of a few such joints on one's person or on one's family tree. Times have changed; gout, though still plentiful, is no longer fashionable; nowadays some students of the disease are finding it difficult even to publicize gout, to dramatize its presence for the sake of its better recognition and its earlier and more effective treatment. If this be so, how much more difficult is it to dramatize the cold, clammy, bluish-white joint of atrophic arthritis, particularly when its possessor is often stagnating in his cripple's room at home or perhaps hidden away in some "chronic hospital" as its none too welcome guest. But if the medical profession is to make notable progress in the scientific and sociologic study of this and other rheumatic diseases, there must be some dramatization of such joints, that more money can be obtained from philanthropists for researches on etiology and treatment, that more money will be assigned by hospital boards to increase the facilities of general and special hospitals for the care of the army of arthritics *before* they are "admissible" to the orthopedic wards as cripples, that funds may be set aside for the long-term treatment of arthritics (some as in-patients, most as out-patients) in stages when the most can be accomplished. Truly one atrophic joint is not of dramatic appeal but millions of them together should be. There are approximately 2,000,000 to 3,000,000 American patients with atrophic arthritis and probably each will possess (before his disease stops) an average of four big and six small, affected joints, making a grand total of 20,000,000 to 30,000,000 aching joints in this group alone, thousands of them on their way to ankylosis.

To be fully successful a campaign against rheumatism needs occasional dramatization. But for the ultimate success of such a campaign a sustained, undramatic, slowly progressing growth of interest in the rheumatic diseases among physicians and laymen is much more important than isolated, sporadic days of high resolve. It is along these lines that the campaigns in this country and abroad are being waged. In the United States, the American Rheumatism Association and the American Committee for the Control of Rheumatism have the important and most cordial support of the American Medical Association, which has opened its programs to an increasing number of reports on the problem of rheumatism. "Hygeia" annually publishes a few papers of special interest to arthritic laymen.<sup>178, 389</sup> The American Rheumatism Association has created associate memberships for interested laymen, social workers, insurance executives, members of professions allied to medicine; to them are being sent bulletins summarizing information of current interest. The Association's Conferences on Rheu-



matic Diseases, held annually at the time of the meetings of the American Medical Association, are increasingly well attended. New Clinical Clubs and small groups of physicians meet, in many of the larger cities, for the purpose of special study of these diseases. New research grants have been made for the establishment of "arthritis units" in several university and city hospitals (e.g. at Harvard University, the University of Michigan, and at Welfare Island, New York City).

In the Commonwealth of Massachusetts, which is perhaps the most progressive in the matter of social legislation, as far as the problem of rheumatism is concerned, an act was recently passed providing for the hospitalization of a certain number of patients, and their treatment for periods as long as six months.

The progress and importance of the campaign in England have been reported by Lord Horder and Sir Frank Fox. The Empire Rheumatism Council purposes to instigate research; to endow chairs or readerships at certain university medical schools for conduct of such research; to enlarge the facilities of special and general hospitals and of hydrologic and radiologic institutions for the treatment of rheumatic diseases and to coöperate with such work in foreign countries; to communicate by lectures and by publications knowledge gained as to the cause of rheumatic diseases and the methods for their prevention, alleviation and cure. Medical science has notably increased the span of a man's life but there is danger that too great a fraction of that lengthened span may be spoiled by the painful symptoms of degenerative arthritis, if not by some more serious articular disability. It is now truly Medicine's duty, having added to the quantity of human life, to add also to its quality. Whatever successes are gained by such campaigns against rheumatism will go a long way toward fulfilling that obligation.

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The chairman of the editorial committee for this review will welcome the receipt of reprints from authors of current (1938-1939) articles which will greatly facilitate the preparation of subsequent reviews.

# CASE REPORTS

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## TULAREMIA; A PATHOLOGIC STUDY OF THE LESIONS IN A CASE TREATED WITH SPECIFIC ANTISERUM, THE PATIENT DYING SUDDENLY FROM INTER-CURRENT CORONARY OCCLUSION\*

By KARL V. KITZMILLER, M.D., F.A.C.P., *Cincinnati, Ohio*

THE increasing prevalence in the use of *Pasteurella tularensis* antiserum, which recently has become commercially available, in the treatment of tularemia, makes the report of a fatal case in which the antiserum was used of special interest at this time. Particularly so, when the fatality is sudden and unexpected, following the antiserum treatment by only a few days. Foshay has stated that in his experience in the specific treatment of these cases he knows of none, with the exception of the advanced, overwhelming infections, in which some associated lesion usually involving the circulatory system has not been responsible for the patient's death. The case herewith reported substantiates this statement. It also offers the first opportunity of observing post mortem the extent and character of the lesions of this disease following antiserum therapy and of comparing them with those of other recorded fatal cases in order to determine, if possible, the effect on healing of the so-called latent lesions, and the relationship of these lesions to the development of immunity to the disease.

The following is a resumé of the history, clinical course† and necropsy record.

### CASE REPORT

The patient, E. R., a white male, mechanic, 36 years of age, was admitted to the Deaconess Hospital, December 19, 1934, complaining of "rabbit fever." He stated that on Tuesday, November 27, he went hunting, killed four rabbits, and that night helped his wife to clean them. Saturday afternoon, four days later (December 1) he complained of feeling achey and weak, and that night had two chills followed by profuse perspiration. He remained in bed until Tuesday, December 4, when he felt well enough to return to work. However, at that time he did not feel so well as usual and had frequent night sweats. About December 12, he noticed some soreness and slight swelling about the outer nail bed of the left thumb, which were present on his admission to the hospital. There was no axillary swelling or soreness nor were there other noteworthy complaints. He had lost 10 lbs. since the onset of his illness, four weeks before (November 27, 1934). There was no history of past serious illness.

Physical examination revealed a very well developed, well nourished man, cheerful, coöperative, not appearing acutely ill, with normal pulse, temperature (97.6° F.) and respirations. There were no physical findings of note recorded except the blood pressure, which was 150 mm. of Hg systolic and 100 diastolic, and a small area of induration and tenderness at the base of the left thumb nail. The following

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From the Pathologic Laboratory, Deaconess Hospital, Cincinnati, Ohio.

† I am indebted to Dr. Harry Box for permission to record these findings.



laboratory findings were noted: Urine negative, except for a trace of sugar in a single specimen; red blood count, 5,520,000, hemoglobin 85 per cent (Dare), white blood count (12-20-34) 9,300; polynuclear neutrophils 28.5 per cent (stab forms 18 per cent, segmenters 10.5 per cent); lymphocytes 61.5 per cent; monocytes 2 per cent; eosinophiles 7 per cent; basophiles 1 per cent. On December 22 the white blood cell count was 8,850; polynuclear neutrophils 50 per cent (stab forms 18 per cent, segmenters 34 per cent); lymphocytes 45.5 per cent; eosinophiles 4 per cent; myelocytes 0.5 per cent. An intradermal test with *Pasteurella tularensis* antigen was positive, December 20.

Agglutination tests were positive (1-640) with *Pasteurella tularensis* antigen on December 21, and again on December 23.

Friday, December 21, two days following admission, the patient was given 15 c.c. of antitularensis serum intravenously with no obvious reaction. The following day 15 c.c. of antiserum were given again with no untoward result. The patient felt very well during his entire hospital stay of five days, his temperature never rising above 100° F. He was permitted to go home December 24, with instructions to return for intradermal testing at weekly intervals. Accordingly, he came to the hospital December 27, 1934, for this test, and at the time remarked that he felt very well and was rapidly gaining his former strength. At six o'clock the following evening, his physician received an emergency call from the patient's wife stating that he had suddenly been seized with cramping pain in the chest and could scarcely breathe. When seen by his doctor he complained of agonizing chest pain, showed evidence of some circulatory collapse. When he had been relieved somewhat by a hypodermic injection of adrenalin, he was immediately taken to the hospital, being admitted at 8:45 p.m. on a stretcher. He had a convulsion shortly after being placed in bed, failed to respond to emergency medication, and died at 8:55 p.m. twenty-eight days after the onset of the disease.

The essential parts of the necropsy protocol follow:

The body was that of a well developed, very well nourished white man, partially bald, with composed features and waxy, sallow facial pallor, apparently about 35 years of age. The skin was pale and elastic with very faint tiny purpuric spots (2 to 3 mm.) over the ankles and insteps. There was some discoloration of the left thumb without swelling, while a clean, dry, linear fissure was present near the base of the nail. The left epitrochlear node was not palpable. The left axillary nodes were discretely enlarged, rather soft and movable, the largest node of this group measuring 3 by 2 by 1 cm. The posterior cervical nodes on the left, and the anterior cervical nodes on the right measured approximately 1 cm. in diameter. There was also a small (1 cm.) palpable node in the right axillary space. The right epitrochlear and the inguinal nodes were not palpable.

The peritoneal cavity possessed a smooth, glistening lining, and contained no free fluid. Numerous fine feathery adhesions extended from the spleen to the inferior surface of the left lobe of the liver. The stomach was of average size, normal contour, and contained a small amount of partially digested food. There was slight uniform edema and softening of the intact, grayish mucosa, with widely spread, fine petechial extravasations, and engorgement of the tiny mucosal and submucosal vessels. The duodenum, of normal size, had a dark, grayish red, softened, edematous lining. There was some softening of the mucosa of the large and small bowel with normal appearing lymphoid structures. The appendix was small and retrocecal, showing no evidence of recent or past inflammation. A group of discretely enlarged, soft, white lymph nodes (1 to 1½ cm.) was found about the common bile duct, duodenum and head of the pancreas. Section showed the majority of these to be completely liquefied, containing milky, puriform fluid.

Cultures taken on blood cystine dextrose agar by Dr. Lee Foshay failed to grow *Pasteurella tularensis*.

The liver weighed 2280 grams, possessed full rounded contours and glistening, thin capsule. The brown and grayish yellow external surfaces were diffusely mottled with grayish patches and streaks. Occurring every 5 to 10 cm. were white, miliary subcapsular foci, measuring 1 to 2 mm. in their greatest extent, surrounded by dark, purplish hyperemic halos 3 to 4 mm. in diameter. Similar miliary lesions, occurring less frequently, were seen on section of the parenchyma. The cut surfaces were everywhere edematous, tawny, softened, granular, and greasy with the normal markings completely obscured. The spleen was enlarged, weighing 330 grams. The capsule was not greatly thickened, but was roughened, granular and of grayish slate color. Section revealed bright, reddish gray, adenoid pulp, with hyperplastic follicles and obscured trabecular markings. Scattered throughout the organ were small focal areas of softening, with a few soft, white, cheesy, necrotic lesions (4 to 8 mm.).

The kidneys together weighed 330 grams, with pale, gray, thin, glistening, tense, readily stripping capsules, and congested subcapsular vessels. The external surfaces were smooth and marked with pressure indentations. On section, the cut surfaces possessed a yellowish, gray, mottled appearance, while the cortex was broad and granular and the striae obscured. The grayish, glistening pyramids had dark red, passively congested borders. The linings of the pelves and ureters were soft and pallid. The bladder was contracted, possessing a pale gray slate-colored, slightly edematous mucosa. It contained a few cubic centimeters of cloudy, straw-colored urine.

The pleural cavities contained no free fluid and possessed smooth, glistening linings, while the grayish white, fully crepitant lungs presented an entirely normal appearance. The peribronchial lymph nodes were small and compact, and the branches of the bronchial tree and pulmonary vessels were not remarkable.

The lining of the pericardial cavity was smooth and glistening, and the small amount of fluid clear and straw-colored. The heart was of average size, weighing 280 grams. The dark, purplish atria bulged prominently, and the left ventricle was flabby and bulbous. There was a small amount of epicardial fat, and an irregularity of the left ventricular wall, as noted on palpation; also a small, thin, tough, fibrinous area in the anterior wall of the right ventricle. The chambers contained dark fluid and recently clotted blood. Advanced subendocardial myomalacia was noted in the right and left ventricular walls, involving portions of many of the papillary muscles. The valvular leaflets and cusps were soft and delicate, while the valvular orifices were of normal size. The heart measurements follow: T.V. 120; M.V. 90; P.V. 75; A.V. 70; T.L.V. 16; T.R.V. 8; T.L.A. 2; T.R.A. 1. The sectioned myocardium possessed glossy, softened, brownish red cut-surfaces, with coarse muscle-bundle markings, and scattered, yellowish gray, and grayish brown foci. There were also frequent focal and linear fibrous scars, with extensive atheromatous plaquing, and partial occlusion of the small coronary arteries. Partial occlusion of the orifices of the right and left arteries was brought about by the encroachment of white and pale yellowish white, slightly elevated, smooth, oval plaques in the sinuses of Valsalva. The coronary vessels were everywhere semi-rigid, projecting noticeably from the cut-surfaces.

There was some atheromatous streaking of the aortic arch and thoracic aorta, with no characteristic linear striations of the intima. Microscopic examination of the heart muscle showed advanced fibrosis with the muscle fibers arranged in a loose connective-tissue meshwork. Many of the individual fibers were hypertrophied with irregular, pyknotic nuclei and fairly well preserved sarcoplasm, while in many subepicardial areas there was complete fibrosis with relatively acellular, hyalinized connective tissue. There was also widespread scarring where a few small fibers remained in very fibrous, cellular connective tissue. A large, healed infarct was seen in the wall of the left ventricle, and also a very fresh infarct showing hemorrhagic necrosis of most of the affected fibers. Nearby was a sclerotic artery with a

small, irregular, fibrinous thrombus incorporating a few blood cells and several particles of brownish amorphous pigment, attached to one side of the vessel wall but not entirely occluding the lumen. Practically all the coronary arteries showed sclerosis with thickening of the intima, hyalinized connective tissue in the muscularis and adventitia, and areas of fatty degeneration and calcification of the intima and media.

The following information was obtained upon microscopic examination of sections from various other organs.

There was some thickening of the pulmonary alveolar walls with scattered monocytes and numerous pigment-laden phagocytes, slight peribronchial fibrosis, active mesarteritis, but no lesions of the lungs characteristic of tularemia.

The liver showed multiple, large, granulomatous lesions with massive caseous centers, radiating peripheral zones of fibroblasts and fibrous connective tissue, occasional large foreign-body giant cells, scattered mononuclear and lymphocytic infiltration, and an outer zone of fairly dense cellular exudate composed largely of mononuclears, lymphocytes, macrophages, a few scattered polymorphonuclear leukocytes, necrotic liver cells and some bile pigment. Around most of these lesions, in the parenchyma, immediately outside the exudate, there were a number of large vacuoles, not taking fat stains and containing varying amounts of yellowish brown and black amorphous pigment, which when scattered or lying near the borders of the larger masses had a spinous, needle-like appearance. (Figure 1.) The pigment failed to show evidence of hemosiderin or iron, with special staining technic. These collections were interpreted as inspissated bile derivatives in dilated canaliculi, occluded as the result of blockage of the local bile circulation near these larger destructive lesions. (Figure 2.) Many liver cells in these areas also contained finely divided bile pigment in the cytoplasm. There were also scattered miliary granulomatous foci without central necrosis and with no, or very little, fibroblastic proliferation. There was much peripheral fibrosis in some of the larger focal lesions, with monocytic and lymphocytic infiltration of the periportal spaces. The portal and hepatic veins contained unusual amounts of dark brownish amorphous and crystalline pigment. The remaining parenchymal cells had pale, mushy, granular, confluent cytoplasm and pale, swollen, vesicular nuclei with prominently bulging membranes and fragmented chromatin.

Focal tularemic lesions similar to those seen in the liver were found in the spleen. There was also active and passive congestion of the pulp with large numbers of monocytes, and areas of hemorrhage associated with marked pigment deposition and pigment-laden macrophages. The capsule was swollen and in places infiltrated with monocytes. The vessels were sclerotic and there was much intravascular, dark brown, partially phagocytized pigment.

In the mesenteric lymph nodes there were massive granulomatous lesions with large caseous centers, peripheral fibrosis, monocytic and lymphocytic infiltration, and numerous foreign-body giant cells. There was also some edema of the pulp with scattered endothelial infiltration.

Sections from the kidneys revealed advanced degenerative changes in the renal epithelium, the cells being pale, poorly stained and confluent, with many missing nuclei. The lumens of the tubules contained pale, granular material, with hyalin casts in some of the collecting tubules. There was much connective tissue in the cortex surrounding groups of dilated tubules, and excessive fibrosis in the medulla, obstructing and obliterating many of the tubules. The glomeruli were large with hyalinized capsules and somewhat shrunken, hyalin-thickened tufts with few nuclei, scattered dark brownish yellow pigment granules, frequent intracapsular adhesions, and occasional small amounts of granular exudate. The vessel walls showed extensive sclerosis, with much dark, brownish pigment in the epithelium of the collecting tubules.

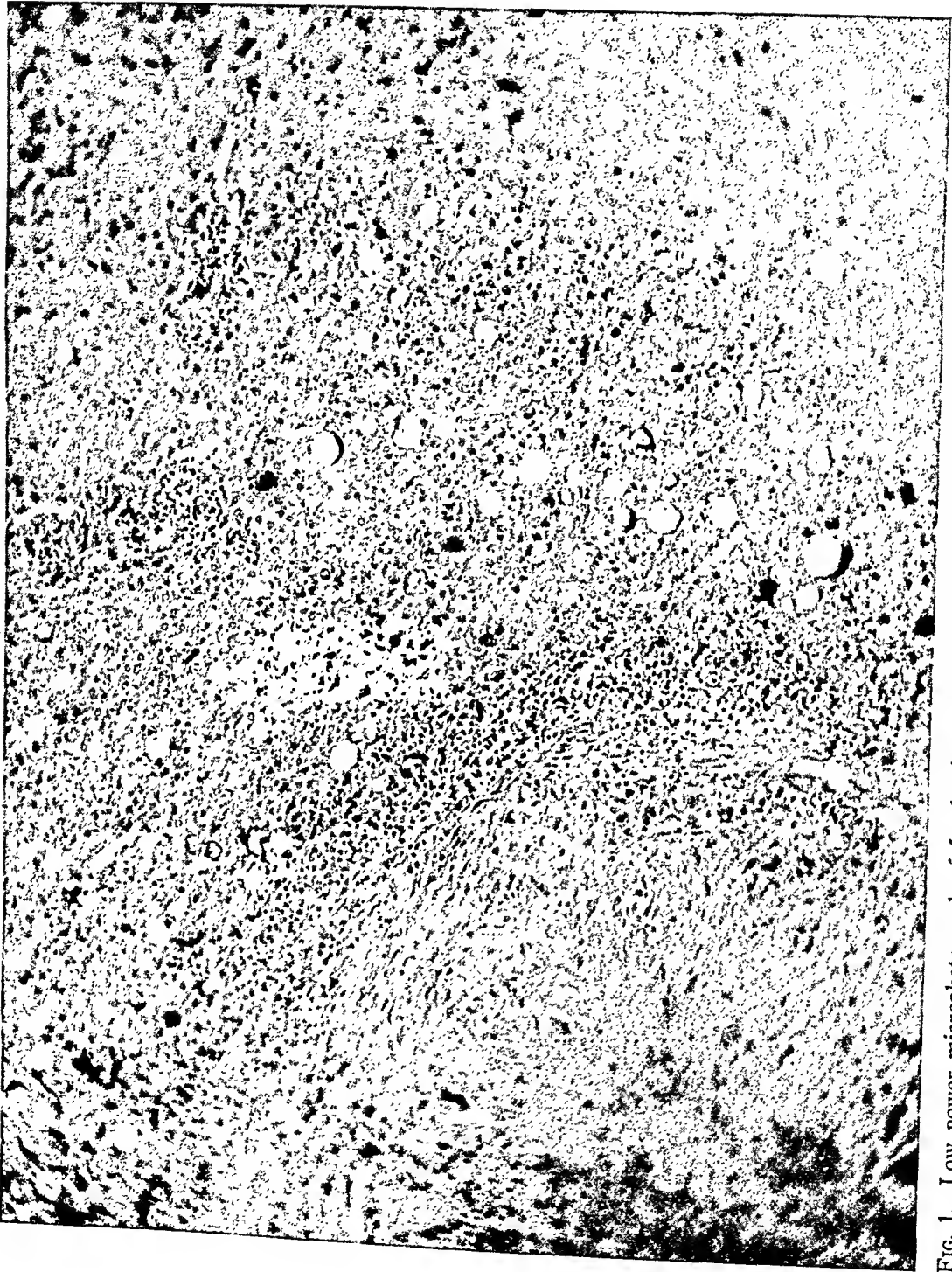


FIG. 1. Low power microphotograph of focal tularememic lesion in the liver, showing dilatation of adjacent bile canaliculi.

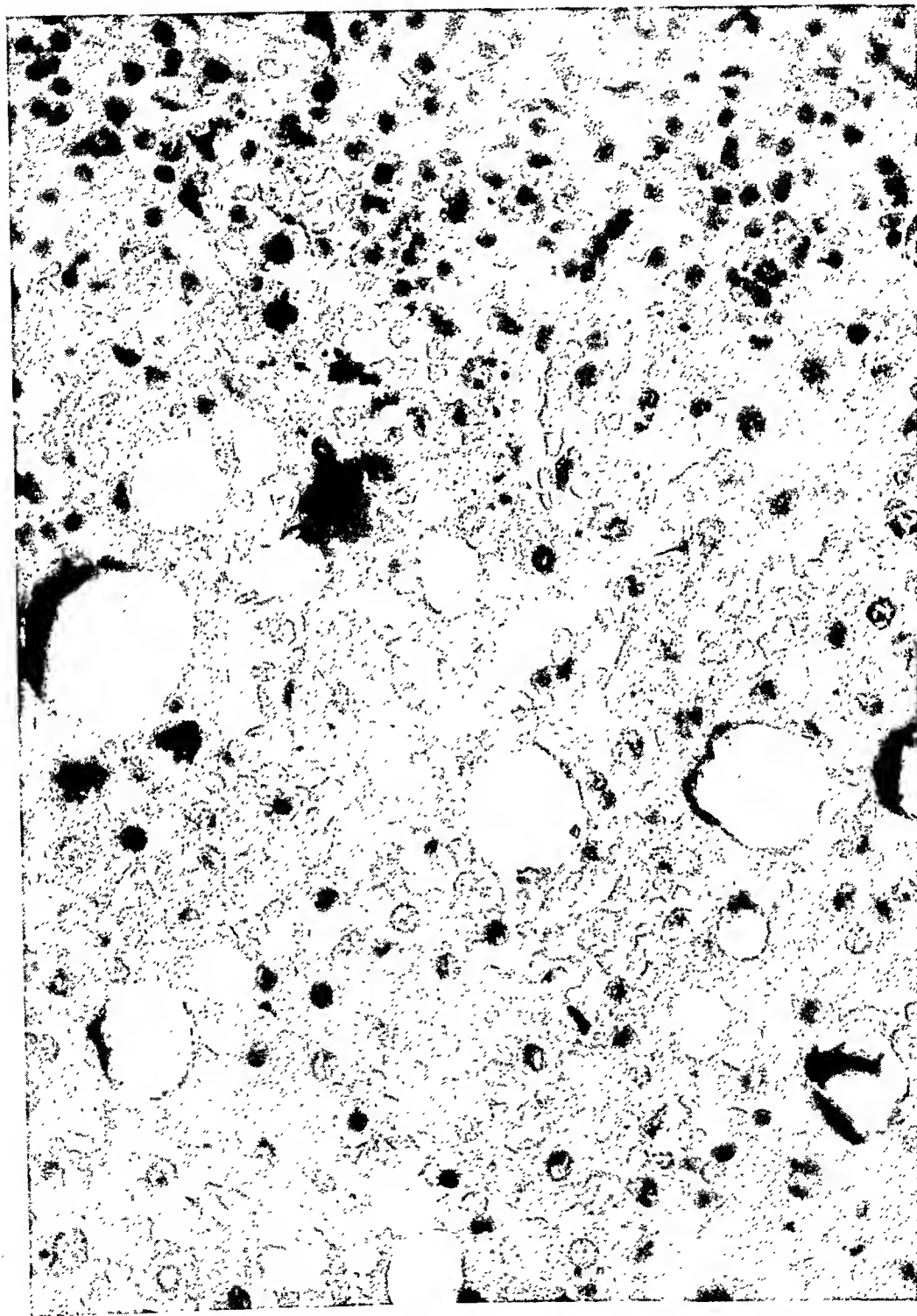


FIG. 2. High power microphotograph of the liver, showing the dilated bile canaliculi containing inspissated bile pigment.

## DISCUSSION

The noteworthy feature in this case is the occurrence of a clinically mild tularemic infection in a young man with seemingly good resistance, who dies suddenly several days after the administration of specific antiserum. Necropsy discloses extensive, severe coronary heart disease as responsible for death, and well established focal tularemic lesions throughout many of the organs of the body, the extent and morphologic character of which would lead one ordinarily to expect an active clinical infection. What rôle the antiserum played is difficult if not impossible to estimate, judging from the character of the lesions alone. These are in all respects similar to those found in the subacute clinical disease of the well defined granulomatous type as it occurs in man. Fibroblastic proliferation and chronic inflammatory cellular exudate are well defined but not sufficiently different from the lesions seen in other non-serum-treated cases to be of significance.

Comment has been made in a previous article\* on the deleterious influence of tularemia on previously damaged hearts. The damage from this infection is apparently due both to toxemic effects on the myocardium and coronaries and to focal lesions which may result in vascular occlusion.

Of particular interest in the pathology of tularemia are the liver lesions noted in this case, certain details of which to my knowledge have not been previously recorded. Aside from the focal and diffuse toxic changes usually seen there are numbers of scattered discrete lesions of the external and sectioned surfaces first noted on necropsy as white miliary, subcapsular foci, measuring 1 to 2 mm. in their greatest extent, surrounded by dark purplish halos, 3 to 4 mm. in diameter. These halos are disclosed microscopically as composed of groups of dilated bile canaliculi containing bile or bile derivatives, and occluded as the result of blockage of the local bile circulation by the large, destructive, caseous lesions in the parenchyma.

## SUMMARY

A case of relatively mild tularemia is presented, the patient dying suddenly of an intercurrent coronary thrombosis shortly following specific antiserum therapy.

Extensive coronary and myocardial disease is disclosed at necropsy as well as the active lesions of tularemia.

Unusual lesions of the liver are discussed.

Nothing in the protocol suggests any untoward effect resulting from the use of the specific antiserum.

\* FOSHAY and MAYER: Viability of *Bacterium tularensis* in human tissues, Jr. Am. Med. Assoc., 1936, cvi, 2141.

## CASE OF MYATONIA CONGENITA TREATED SUCCESSFULLY WITH ADRENAL CORTEX (ESCHATIN) \*

By MAX H. WEINBERG, F.A.C.P., M.D., *Pittsburgh, Pennsylvania*

*Myatonia congenita* has attracted a great deal of attention, in spite of its comparative rarity, ever since the condition was first described by Oppenheim in 1900. In 1917 Reuben<sup>1</sup> could gather from the literature only 130 cases and reported on six of his own, the highest number reported by one observer. The majority of the reports deal with but one or two cases. Most of the reports are concerned only with description of the disease and the central point of the discussion is, usually, whether it is a separate entity or merely another manifestation of the Werdnig-Hoffman type of infantile muscular atrophy. Very little has been written about treatment. The usual statement is that there is no treatment other than palliative, and that although a certain amount of improvement does set in in some cases, no case is known in which the patient walked again without ataxia or a "waddle" (Kerley and Blanchard,<sup>2</sup> Shuman<sup>3</sup>). Reuben<sup>1</sup> makes the emphatic statement that "The prognosis as to recovery is absolutely bad; there is no record of a complete recovery in a single case." He points out that of infants of one year or less suffering with this disease, whose fate is known, 70 per cent died, and adds: "One cannot understand why it is, in the face of these statistics, that many writers give such a favorable prognosis in this disease."

The rarity of *myatonia congenita*, and the complete recovery of our patient on a specific type of therapy have led the writer to report the following single case in order that the treatment may be tried by other observers, who may have the opportunity to see more patients suffering with the condition.

### CASE HISTORY

B. J. S., a female child, aged 20 months, was admitted to the hospital on January 15, 1937, with a history of inability to stand or walk for the past four weeks, sleeplessness, and restlessness for the past three or four months. Around the middle of December 1936, the mother noticed a gradual development of weakness in the lower extremities which progressed to a complete loss of motor function. A gradual weakness of the arms was also observed, but to a lesser degree.

Neurological examination revealed an apparently well developed child; closed fontanelles; rapid pulse; excessive perspiration; normal cranial nerves; practically complete loss of the deep reflexes of the arms, and complete loss of those of the lower extremities; marked hypotonia of all the extremities; flail-like joints of the legs especially—the legs could be brought up easily and the feet placed back of the neck; and complete inability to walk, stand, or even turn over in bed.

A diagnosis of *myatonia congenita* (Oppenheim) was made.

Electrical tests gave the typical reaction of myatonia. Dr. H. Jacox reported as follows: "Electrical muscle testing reveals a most unusual condition. The child is able to withstand the full output of faradism without crying. This dose is larger than the normal adult can stand. However, there is response in both thighs to only the strongest galvanic current over the motor points. We did not get much response to faradism in the thighs, although we did in the legs. The condition is less marked in the upper extremities."

\* Received for publication January 26, 1938.

From the Neurological Service of the Western Pennsylvania Hospital.



For a few days the child had a rise in temperature, on two occasions as high as 102° F. The laboratory tests were essentially negative with the exception of a moderate relative lymphocytosis, 43 per cent small, and 11 per cent large lymphocytes.

Because of theoretical considerations, it was decided to use an adrenal cortex extract (Eschatin\*) by subcutaneous injection. The child lived a distance from the city, and because of the parents' insistence on taking the child home, it was decided to have the family physician, Dr. D. Gordon Jones, carry out the treatment.

The dosage given was as follows: Three injections of ½ c.c. Eschatin, three times a week for six weeks; two injections weekly for six weeks; and one to two injections weekly for eight weeks.

On March 16, 1937, five weeks after initiation of the treatment, the mother wrote, "She can use arms and fingers real good, and can almost turn in bed. She can take two steps with left foot, but drags right foot. Can also feed herself."

Reëxamination on April 5, 1937 revealed that hypotonia and flail joints were still present, but that the patient could move her legs voluntarily. She cried and resisted so much, however, that her gait could not be tested, although the mother stated that the child could take steps without any support.

Unfortunately, once the child improved, the people refused to coöperate any further. We could not induce them to bring the child to the city for another neurological examination or electrical testing, which we were particularly eager to do.

December 12, 1937. Reëxamination at the patient's home:

Mother states that the child walks to the center of the town, a distance of half a mile, frequently. The last symptom she observed was a difficulty which the child experienced in getting up from the floor, mostly "a stiffness in the hip joints," and that at times it is noticeable even now when the child is tired.

The child is very well developed. She walks normally, and uses her arms well. On having her rise from the floor, no difficulty is discernible. There is no hypotonia. The deep reflexes of the arms are diminished. The patellar reflexes are absent. The Achilles jerks are present and within normal limits.

### DISCUSSION

The writer is fully cognizant of the fact that one successful case does not justify making any claims, but on theoretical grounds it seems that this treatment offers something definite in the condition under discussion.

The reasoning that was followed for the use of adrenal cortex was based on the fact that only recently quinine was found by Wolf<sup>4</sup> to be practically a specific for *myotonia congenita* in his first report of four cases. This was corroborated by Smith,<sup>5</sup> and another series of four cases of *myotonia congenita* and *atrophica* was reported by Kennedy and Wolf<sup>6</sup> with good results. I started out from the premise that *myotonia congenita* is the very opposite condition of *myotonia*. This is obvious, of course, primarily by the hypotonia as contrasted with the markedly increased tone in *myotonia*, and secondly, by the electrical reactions. In *myotonia congenita*, the resistance to electrical currents, especially the faradic current, is well known and even considered of great diagnostic importance; whereas in *myotonia congenita*, the resistance to electrical current is much diminished. I, therefore, decided to use adrenal cortex which is known to be an antagonist to quinine.

While there is a definite pathological picture in this condition pointing to changes in the cord and anterior roots, as well as in the muscles, there is a difference of opinion as to the rôle this plays in the disease. It is believed by

\* Parke Davis and Co.



some that the neuro-pathologic changes are secondary to the disease in the muscular apparatus, and that the changes in the anterior horn cells, the occasional changes in the twelfth nucleus and motor roots are due to lack of stimulation resulting from the inactive muscles. Reuben<sup>1</sup> states it thus: "To us it appears that the pathogenesis of this disease is to be sought in a primary abiotrophy of the musculature, and a secondary failure of proper development of the whole nervous system (cerebrospinal axis and peripheral nerves) brought about by deficient natural stimulation to its growth by the abiotrophic musculature." Albanese,<sup>7</sup> more recently, in offering an explanation for the improvement in the frequently seen contractures, as a result of orthopedic measures, says: "Most authors seem to agree that the cause of *myatonia congenita* is a hypogenesis of the peripheral spino-muscular neurons—the cause being so far unknown—which acts during embryonal development." He then goes into a discussion of "triple tonic innervation" as advanced by Luisada, and the muscle changes described by Fiore and Guidi, and concludes that changes take place in the terminal plaques of Boeke. As additional proof of the tone disturbance originating peripherally, he adduces the fact that in many cases of *myatonia congenita*, in the presence of marked deficiency of tone, muscular contractility is well preserved. He concludes his argument with the following statement: "In such a manner, we can state that the successive improvement is due partly to peripheral stimuli resulting from the establishment of activity, be it ever so limited, of the muscular function. In this manner, we could bring about the cure in tendons not only in invigorating the nascent functions of muscular tone, but also in reawakening the contractile functions."

One more link in the chain of evidence is the fact, more recently established by Richter and Levine,<sup>8</sup> that following sympathectomy, there is an increase in the electrical resistance of the skin. One of the most characteristic symptoms of *myatonia congenita* is a marked increase in resistance to electrical currents. It is conceivable, then, that there may be in this condition a marked disturbance of the sympathetic system as a whole, including the adrenals. Bing,<sup>9</sup> states that the adrenal has been "denominated directly as the 'accessory apparatus of the sympathetic.'" Howell<sup>10</sup> states: "Langley has called attention to the peculiar fact that the action of adrenal extracts or solution of adrenalin on plain muscles resembles always the effects of stimulating the sympathetic nerves supplying the same tissue." And again (p. 844) "Removal of this secretion—adrenalin—results in a marked loss of muscular tone and vigor, exhibited by the blood vessels, the heart, and the skeletal muscles, and death follows rapidly." Many cases of *myatonia congenita* have developed after an acute infection. Indeed, this case that I am reporting had some sort of an obscure infection as was evidenced by the rise in temperature. It is well known, also, that infections are frequently followed by transient hypoadrenemias. Thaddea,<sup>11</sup> as reported in the Year Book of Neurology and Psychiatry 1935, calls attention to the deleterious effect of infection in Addison's disease. The Year Book Editor's comment on this work is as follows: "Thaddea's two papers point out not only the intimate connection between adrenal cortical function and carbohydrate metabolism, but also the way in which infections probably reduce cortical function temporarily."

It is reasonable, then, to postulate that *myatonia congenita* is perhaps due to a poorly developed sympathetic system more defective in certain cases than in

others; that in some it takes an infection to precipitate the condition, whereas in the more severe cases, the condition manifests itself very early in infancy independent of an aggravating infection.

I believe that it is for this reason that Eschatin proved so beneficial in this case. It is because of its potency as a cortical extract that I selected it for trial, and the results in this case, at least, are striking. Whether it will be equally as effective in cases occurring spontaneously without infection remains to be determined. Other endocrine products, including epinephrine had been previously tried but with indifferent results. The writer feels that the results obtained in this case warrant further trial of adrenal cortical extracts.

If the assumption that the condition is primarily the result of a faulty development of the entire sympathetic system bringing about changes in the central nervous system because of lack of stimulation from the musculature is correct, it stands to reason that the earlier the treatment is instituted, the less damage will have taken place, and the better will be the chances of beneficial results.

### CONCLUSIONS

1. A case of *myotonia congenita* (Oppenheim) is reported, which recovered fully while under treatment with adrenal cortex (Eschatin) over a period of about five months.

2. A theoretical basis for this treatment is advanced, namely:

- a. That this condition being clinically the opposite of *myotonia congenita* for which quinine seems to be a specific, should respond to the treatment with the antagonist to quinine, and,

- b. That the condition seems to be due to a disturbance of at least certain parts of the sympathetic system.

3. It is hoped that other observers who have an opportunity to see such cases will try this treatment.

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## EDITORIALS

### *THE POSTGRADUATE COURSES*

Many members of the College are probably debating still the advisability of attending one or another of the postgraduate courses which have been arranged for their benefit in St. Louis, Chicago, Nashville and Baltimore. Each member of the College has received a program which contains most of the important data. A survey of these courses can not but impress one with the opportunity they offer for a concentrated review of certain fields of internal medicine.

One of the outstanding features of the annual Sessions of the College has always been the visits to the various clinics in the city in which the meeting was held. This opportunity to see "work in progress" and to meet the men who were making notable contributions in various fields is a part of the Sessions especially cherished by many of the members. In a sense, the Postgraduate Courses are an extension and an intensification of this same form of educational experience.

Those who decide to attend will have for a period of one or two weeks the experience of forming part of a small group for whose benefit all the resources and all the latest information of one or more of the leading medical schools of the country will be systematically made available. The stimulus of close contact with the working methods of these institutions, and with their outstanding teachers, and the privilege of informal discussion of clinical or scientific subjects will be theirs.

A study of the program reveals that each course varies somewhat from all the others as to the amount of didactic work, the opportunity to study cases, the amount of time devoted to the underlying scientific bases of clinical medicine. Each man may find what he feels that he most requires.

The enthusiastic reception given to last year's courses is the best guarantee that those who attend this year's will likewise feel that to take part in this aspect of the College's work is one of the most valuable privileges of the Fellows and Associates.

### *SURGICAL THERAPY IN CONGENITAL INTRACRANIAL ANEURYSMS*

Intracranial aneurysms due to congenital weakness of the arterial wall occur chiefly at the base of the brain on the vessels forming part of the circle of Willis, or on closely adjacent arterial trunks. There is a marked tendency for such aneurysms to develop at the site of vascular bifurcation or branching. At these sites congenital defects of the elastic and muscular elements of the arterial wall occur. The aneurysms are occasionally multiple in the same individual. They show great variations in size but the majority are small, like a "minute berry growing from a stem."<sup>1</sup> The occurrence of

<sup>1</sup> FORBES, W. D.: On origin of miliary aneurysms of cerebral arteries, Bull. Johns Hopkins Hosp., 1930, xlvii, 239-284.

this stem between the artery and the main aneurysmal dilatation is a point of importance and the frequency of its occurrence at different stages of development of the aneurysm needs further study.

We are in need also of further data concerning the relative frequency of occurrence of the congenital type of aneurysms on the individual arteries. From the point of view of accessibility and of the possible effects of ligation it is of importance whether an aneurysm arises from the basilar artery, from the internal carotid proximal to the circle of Willis, from the circle of Willis itself, or from such arteries as the middle cerebral, anterior cerebral, etc., at points distal to the circle of Willis. Various compilations from autopsy records are available but they rarely distinguish clearly between the small congenital lesions and the various aneurysmal dilatations due to vascular degeneration in the aged. We do not know clearly what proportion of the total number of congenital aneurysms lie in situations now accessible to direct surgical attack, or where they might be influenced by extra- or intracranial carotid ligation.

Congenital aneurysms may present symptoms before they rupture; or fatal bleeding may be the first clinical event; or there may be repeated attacks of subarachnoid hemorrhage with or without the presence of localizing symptoms between the attacks.

From the point of view of improving the therapeutic outlook the group of cases showing symptoms before rupture is that which deserves the most careful attention. Unfortunately, for the most part such symptoms are seen only in cases in which the aneurysms are of considerable size, but this is by no means always the case. A very small lesion if located in close relation to the course of the cranial nerves may cause localizing symptoms. In most instances of this kind, so far, the clinical diagnosis has been brain tumor rather than aneurysm. Borchartd<sup>2</sup> reported 11 craniotomies by well known neurosurgeons in various countries in which quite unsuspected intracranial aneurysms were discovered. However, in an increasing number of instances the diagnosis of intracranial aneurysm is being suggested because of characteristic localizing signs, prior to the occurrence of the syndrome of subarachnoid hemorrhage. Most of such cases are aneurysms of the internal carotid whose ophthalmoplegic and visual tract effects have been carefully studied (Jefferson<sup>3</sup>). Aneurysms of the internal carotid in the cavernous sinus or just at the point of exit produce oculomotor paralyses (III, IV, VI) and not infrequently severe orbital and head pain (V) on the side of the lesion. Anesthesia in the area of distribution of the ophthalmic division of the fifth nerve is also characteristic. The anatomical relations of the cavernous sinus readily explain such effects. Those aneurysms arising from the internal carotid between its exit from the cavernous sinus and its junction with the circle of Willis are more apt to produce ocular syn-

<sup>2</sup> BORCHARDT (ref. SCHMIDT, HANS): Aneurysmen der Hirnarterien, etc., in Krause: Die Spezielle Chirurgie der Gehirnkrankh.

<sup>3</sup> JEFFERSON, GEOFFREY: Compression of the chiasma, optic nerves and optic tracts by intracranial aneurysms, Brain, 1937, ix, Part 4, 444-497.

dromes of chiasmal or prechiasmal type with characteristic field defects. Jefferson calls attention also to the frequency of mental symptoms.

There are also available many instances of vertebral and basilar aneurysms with suggestive localizing signs arising from pressure on the seventh, eighth, ninth and tenth nerves as well as from pressure on the motor tracts and medullary centers. These, however, have usually been arteriosclerotic fusiform aneurysms rather than saccular congenital lesions and hence have little therapeutic interest.

Since congenital intracranial aneurysms are not of exceptionally infrequent occurrence as compared to other space-occupying lesions, their presence should be suspected when localizing symptoms of the above mentioned types are discovered in the clinical examination. Further help in diagnosis may be obtained from observation of spontaneous remissions in the symptoms over considerable periods of time and of exacerbations associated with sudden and severe head pain. Such attacks are not necessarily associated with the full syndrome of subarachnoid hemorrhage.

Rupture of the aneurysm with sudden and rapidly fatal subarachnoid hemorrhage, or hemorrhage into the brain substance, may terminate a period characterized by such localized signs as those above described, or may occur as the first evidence of the presence of an aneurysm.

However, in a considerable percentage of cases the first hemorrhage or leakage is not fatal. A patient in whom spontaneous subarachnoid hemorrhage has been recovered from, therefore presents interesting diagnostic and therapeutic problems. Since rupture of an intracranial aneurysm is by far the commonest cause of spontaneous subarachnoid bleeding it is important to search for the localizing signs which would indicate the site of the leaking aneurysm. From the history, or from observations made in the period preceding the attack a clue may be obtained in some cases. Even more frequently the extravasated blood about the aneurysm will have produced the first evidence of pressure effects. In many instances, however, no such localizing symptoms are discoverable either before or after the attack.

It is evident that since intelligent therapy depends upon localization of the lesion, further data than those furnished by the pressure effects of the aneurysm itself or of the peri-aneurysmal clot are highly desirable.

Sossman and Vogt<sup>4</sup> first called attention to certain roentgenographic appearances which may be helpful in diagnosing aneurysms of the intracranial portion of the internal carotid artery. These depend upon (1) calcification in the wall of the aneurysm which when present may show as thin semilunar shadows, convexity upward, lying alongside the sella and (2) erosions of bone by the aneurysm usually involving one or both clinoids on one side and a part of the sphenoid body on the same side. Others have confirmed the occasional value of these signs.

The development of cerebral arteriography by Egas Moniz<sup>5</sup> has led to a wide use of this method in certain clinics, chiefly foreign, for the study of

<sup>4</sup> SOSSMAN, M. C., and VOGT, E. C.: Aneurysms of the internal carotid artery and the circle of Willis from a roentgenological viewpoint, *Am. Jr. Roent. and Rad. Ther.*, 1926, xv, 122.

<sup>5</sup> MONIZ, EGAS: *Angiographie cérébrale*, Paris, 2nd edit., 1934.

cerebral vascular anomalies, aneurysms, vascular tumors and displacements of brain substance by space-occupying growths. The opaque medium now used, thorotrast, is injected into the carotid (common or internal) and immediate roentgenograms of the skull then will show outlines of the anterior group of arteries. In a considerable number of cases the presence and exact site of a congenital sacculated aneurysm has been well demonstrated by this means.<sup>5, 6, 7, 8, 9, 10</sup> Even the important detail of the presence of a pedicle may at times be shown. Aneurysms in surgically accessible areas are those most apt to be well visualized by carotid injection.

The disadvantages of cerebral arteriography are obvious. Some have punctured the carotid artery through the skin but more usually the artery has been exposed,—an operative procedure which, at least for those who prefer injecting the internal carotid, often presents considerable difficulty. The timing of the injection and of the exposure of the film is a highly technical matter. Finally there is an undeterminable factor of risk which comes from the storage of the thorotrast in the body. On the other hand many hundreds of such injections have now been made yielding successful arteriographs and unaccompanied except in a very small per cent of cases by any detectable reaction. As for the late consequences from the alpha ray activity it is still too early to state what these may prove to be. However, since the amount of thorotrast injected is quite small (8–12 c.c.) in comparison with the amount (75 c.c.) used in hepato-lienography and since Yater<sup>11</sup> and others after extensive experience with the latter method over a number of years have not seen late harmful effects it may be said that the risk in cerebral arteriography is minimal as compared to the dangers of intracranial aneurysm.

The surgery of intracranial congenital aneurysms is still, relatively speaking, in its infancy. The methods available are (1) ligation of the internal carotid in the neck on the side of the lesion; (2) supracavernous intracranial ligation of the internal carotid; (3) ligation of branches of the circle of Willis on either side of an aneurysm; (4) clip ligation of the pedicle of a carotid aneurysm.

Ligation of the internal carotid in the neck is currently the most frequently applied procedure. It is evident that its best chance of success is limited to intracranial aneurysms of the carotid trunk below the circle of

<sup>5</sup> BRAMWELL, E.: Leaking aneurysm as a cause of third nerve paralysis with special reference to two cases in which diagnosis was confirmed by arterial encephalography, *Trans. Ophth. Soc. U. Kingdom*, 1934, liv, 205.

<sup>7</sup> NORTHFIELD, D. W. C.: Observations on the clinical indications for cerebral arteriography, *Lisboa Médica*, 1937, xiv, 861–872.

<sup>8</sup> HERMANN, K., OBRADOR, S., and DOTT, NORMAN M.: Intracranial aneurysms and allied clinical syndromes: cerebral arteriography in their management, *Lisboa Médica*, 1937, xiv, 782–810.

<sup>9</sup> TÖNNIS, W.: Die Bedeutung der "Angiographie cérébrale" für die Indikationsstellung zur Operation von Hirngeschülsten, *Lisboa Médica*, 1937, xiv, 773–780.

<sup>10</sup> RIECHERT, T.: Kreislaufstörungen im Hirn im Arteriographischen Bild, *Ztschr. f. d. gesam. Neur. u. Psych.*, 1938, clxi, 426–429.

<sup>11</sup> YATER, W. M., OTELL, L. S., and HUSSEY, H. H.: Hepatosplenography with stabilized thorium dioxide sol: a follow-up study of 200 patients examined over a period of five years, *Med. Ann. Dist. Col.*, 1936, v, 241.

Willis. Its danger lies in the possibility that the collateral circulation through the circle of Willis may be insufficient to supply the brain on the side of the ligation, or that ascending thrombosis may result in occlusion in the communicating arteries. Temporary carotid occlusion affords some opportunity for estimating the collateral circulation but can hardly offer dependable assurance of its efficiency. The reality of the danger is shown by a series of fatalities or permanent paralyses which have followed this ligation. Da Costa estimates that 20 to 25 per cent of carotid ligations develop evidence of intracranial damage. On the other hand there have been a number of successes reported in instances of intracranial aneurysm. Only prolonged observation, however, can show how permanent such cures will be. It is evident that the dangers of carotid ligation are less in younger patients. The fact that many congenital aneurysms come to treatment under 40 years of age has a bearing on this point.

The intracranial supracavernous ligation of the trunk of the internal carotid has been employed in conjunction with neck ligation of the same vessel as a means of controlling the traumatic arteriovenous aneurysms in the cavernous sinus. It has not been applied to saccular aneurysms.

In 1936 Norman Dott of Edinburgh localized by arteriography a small aneurysm at the junction of the left anterior cerebral artery and the anterior communicating artery. He was successful in applying silver clips to the anterior cerebral on both sides of the aneurysm. The patient died of a postoperative mishap before the effects could be estimated. W. Tönnis of Berlin refers briefly to an aneurysm of the anterior communicating artery which he localized by arteriography and successfully operated upon in 1935. Recently (1938) Dandy<sup>12</sup> has reported a brilliant success in a case of congenital aneurysm, which was diagnosed clinically and localized by Ford prior to frank rupture, on the basis of sudden severe pain in the right frontal region and right eye followed by rapidly progressive paralysis of the right third cranial nerve. Using his hypophyseal approach Dandy found a pea sized aneurysm arising by a narrow neck from the suprasellar portion of the right internal carotid and resting upon the third nerve. He was able to apply a silver clip on the neck of the aneurysm flush with the wall of the internal carotid. Recovery followed.

It is evident that this procedure when applicable is the optimal one. Study of the reproductions of arteriographs now in the literature suggests that such an opportunity may be relatively frequent in this group of cases.

A new field for surgical treatment of congenital intracranial aneurysms is now in process of development. More detailed study of the symptomatology of these cases before and after rupture may lead to more frequent use of cerebral arteriography as an aid in determining the exact site, the configuration and the size of the lesion. Only upon such a basis can the question of operability, and of the most suitable type of operation be best decided.

<sup>12</sup> DANDY, WALTER E.: Intracranial aneurysm of the internal carotid artery: cured by operation, *Ann. Surg.*, 1938, cviii, 654-659.

## REVIEWS

*A Primer for Diabetic Patients.* By RUSSELL M. WILDER, M.D. 191 pages; 12 × 18 cm. W. B. Saunders Co., Philadelphia. 1937. Price, \$1.75.

This familiar diabetic manual, first introduced in 1921, is now its sixth edition. The revision was especially necessary because of the introduction of protamine zinc insulin in the treatment of diabetes. The section dealing with the definition of diabetes should be read by all patients before starting any form of treatment. Sections dealing with the various complications are excellent, particularly the chapter pertaining to the care of the feet. The charts and food tables included in the text are of aid to both patient and physician.

As stated in the preface, "this book is addressed to the patient who is working out a life complicated by diabetes under the guidance of his family physician." This should not discourage the physician from reading the manual, as most valuable information can be obtained in a clear concise manner.

J. S. E.

*Hematology.* By WILLIAM WAGNER, M.D., D.P.H. 395 pages; 23 × 15 cm. P. Blakiston's Son and Co., Inc., Philadelphia. 1938. Price, \$4.50.

In writing this book the author has kept in mind the needs of the practising physician as well as those primarily interested in the study of disease by laboratory methods. In general the subject is treated along conventional lines.

The author has devoted special attention to the formation and removal of the blood cells, and the more important theories as to the derivation of the cells are adequately considered. The gross and microscopic anatomy of the hemopoietic tissues in normal and pathological conditions is well covered. The morphology of the cells in stained preparations is well described, but very little attention is given to fresh moist preparations. A chapter of 28 pages is devoted to the technic of the usual simpler laboratory procedures, including sternal aspiration. The technic of supravital staining of leukocytes is not given.

The pathogenesis of the different types of anemia is particularly well discussed, with special emphasis on the part played by the various deficiencies. The anemia following poisoning with benzol and with radioactive substances is also fully discussed. The various diseases of the blood are individually considered, with good descriptions of the clinical symptoms as well as the hematological and pathological features.

The book contains 23 illustrations and 3 colored plates. Although these are for the most part fairly good, they are not up to the standard of the text. The book is up to date and most of the newer work has been included. It is interestingly written, and should be a useful reference book for students and internists.

P. C.

*Synopsis of Genito-Urinary Diseases.* By AUSTIN I. DODSON, M.D., F.A.C.S. 294 pages; 13 × 20 cm. C. V. Mosby Co., St. Louis. 1937. Price, \$3.00.

This is an amazing little book of 294 pages that covers the entire field of this surgical specialty in a surprisingly complete way. It has already gone through two editions. The second edition has been revised to include a discussion of diets influencing infections and calculus formation. Glandular therapy is also introduced and the whole book brought into line with the very newest monographs.

The very simple but very definitive illustrations are ample and clear.

This book contains the essentials that are of value to the internist interested in urology.

W. H. T.



*The Fundamentals of Internal Medicine.* By WALLACE M. YATER, A.B., M.D., M.S. (in Medicine). 1021 pages; 25 × 17 cm. D. Appleton-Century Company, New York. 1938. Price, \$9.00.

In his introduction to this new text, Dr. Yater says that it is designed primarily for the introduction of students to the subject of internal medicine, presenting the minimum amount of knowledge of clinical medicine a medical student or general practitioner should have at his fingertips. Most of the subject matter has been written by Dr. Yater himself, but eleven other authors have also contributed.

The reader is impressed by the book's brevity, clearness, orderliness and lack of confusing overdiscussion. Introductions to the different sections are written so that manifestations of diseases may be correlated with others in the same general groups. Symptomatology and differential diagnosis are stressed by means of diagnostic tables, outlines, and grouping of symptoms that are common to certain classes of disease. Presentations, however, are not from symptomatic, but from etiological and anatomic viewpoints.

The author has followed the English custom of including a chapter on diseases of the skin. There is also a short section on diseases of the ear by F. C. Schreiber, and one on diseases of the eye, by J. A. Greear. These three unusual chapters are intended to correlate knowledge of these specialties with the subject of internal medicine.

Illustrations are used freely, and are uniformly excellent. The publishers should be congratulated on the roentgen-ray reproductions.

"Fundamentals of Internal Medicine" may be fully recommended to medical students. In the reviewer's opinion, it is a valuable addition to our teaching texts.

T. N. C.

*The Diary of a Surgeon in the Year 1751-1752.* By JOHN KNYVETON; edited by ERNEST GRAY. 319 pages; 21 × 15 cm. D. Appleton-Century Company, New York. 1937. Price, \$2.50.

This is a gripping story of surgical training and adventure of a ship's surgeon on the high seas, equally interesting for the laity and for members of the medical profession.

The basis of the story is a period in the life of one John Knyveton whose adventures have been recorded and edited in diary form by Ernest Gray.

The book consists of two parts, the first dealing with the apprenticeship and training of Knyveton in London as a surgeon, which took the lengthy time of six months. An intimate account of the conditions of the time—thrilling tales of grave robbing for suitable cadavers, of the filth of the infirmaries, of numerous amputations with nothing to allay pain, of the appalling hospital death rate. There are occasional periods of diversion with fellow students, walking, conversation at taverns, and trips to the theatre. This Part ends with the student out of funds and successfully qualified for Surgeon's Mate.

The remaining part of the year is spent in His Majesty's service as Surgeon's Mate on the frigate Lancaster. His experiences at this post are exciting. He tells of trouble with scurvy, terrible storms, bloody fights with pirates, and his work on a Spanish isle treating tropical fever. Throughout he is a hard working, honorable and admirable character.

Regardless of the authenticity of the subject matter, this is a thrilling, fast moving, enjoyable book.

H. C. H.

*Fearfully and Wonderfully Made.* By RENÉE VON EULENBURG-WIENER. 472 pages; 16 × 24 cm. Macmillan Co., New York. 1938. Price, \$3.50.

The author, trained primarily in the basic sciences, views the functioning of the human organism, as far as possible, upon an atomic structural basis. The book is constructed about the hypothesis that the obscure and experimentally elusive phenomenon of cellular specificity of function is based upon molecular asymmetry, —the consequent molecular instability affording a readily available source of electrodynamic energy. The attempt is made to apply this explanation to the metabolism of carbohydrates, proteins, and fats, hormones, vitamins, muscle, nervous system, special senses, etc.

The book is written in a readable style and will be most interesting to those who enjoy such speculations.

E. F. C.

## COLLEGE NEWS NOTES

### NEW LIFE MEMBERS

Announcement is made of the following additional Life Members of the American College of Physicians, recorded in the order of the receipt of subscriptions:

Dr. O. H. Perry Pepper, Philadelphia, Pa.  
Dr. Charles Hartwell Cocke, Asheville, N. C.  
Dr. Andrew Henry Hangarter, Brooklyn, N. Y.  
Dr. Richard Arminius Kern, Philadelphia, Pa.  
Dr. Edward Bridge Bigelow, Worcester, Mass.  
Dr. William Simmons Baldwin, Lorain, Ohio  
Dr. James Bryan Herrick, Chicago, Ill.  
Dr. Lawrence Getz, Ancon, C. Z.  
Dr. Clifford P. Rutledge, Shreveport, La.

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### GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of publications by members are gratefully acknowledged:

#### *Reprints*

Dr. Nathan Blumberg, F.A.C.P., Philadelphia, Pa.—1 reprint;  
Dr. Walter Clarke, F.A.C.P., New York City—2 reprints;  
Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh, Pa.—1 reprint;  
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;  
Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—January, 1939, Supplement to "Modern Drug Encyclopedia and Therapeutic Guide";  
Dr. Charles M. Griffith, F.A.C.P., Medical Director of the U. S. Veteran's Administration, sent for the College Library a copy of "A Study of Silicosis" by Dr. Philip B. Matz, F.A.C.P., deceased;  
Dr. M. Coleman Harris, F.A.C.P., New York City—1 reprint;  
Dr. Cullen Ward Irish, F.A.C.P., Los Angeles, Calif.—1 reprint;  
Dr. Robert F. Ives, F.A.C.P., Brooklyn, N. Y.—1 reprint;  
Dr. Harold R. Keeler, F.A.C.P., Philadelphia, Pa.—1 reprint;  
Dr. Donald S. King, F.A.C.P., Brookline, Mass.—5 reprints;  
Dr. Hubert C. King, F.A.C.P., Lakewood, Ohio—1 reprint;  
Dr. Albert H. Rowe, F.A.C.P., Oakland, Calif.—2 reprints;  
Dr. Lowell S. Selling, F.A.C.P., Detroit, Mich.—3 reprints;  
Dr. G. Louis Weller, Jr., F.A.C.P., Washington, D. C.—7 reprints;  
Dr. John H. Willard (Associate), Philadelphia, Pa.—1 reprint;  
Dr. Edward E. Woldman (Associate), Cleveland, Ohio—1 reprint.

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### EASTERN PENNSYLVANIA SECTIONAL MEETING

Under the Governorship of Dr. Edward L. Bortz, F.A.C.P., Philadelphia, the first sectional meeting of Fellows and Associates of the College from Eastern Pennsylvania was held at Philadelphia, on February 3, 1939. Pennsylvania is divided at 78° longitude and the eastern portion is assigned to the Governorship of Dr. Bortz. The program showed a certain amount of novelty and originality, the meeting being referred to as a "ROUND-UP" and divided into four portions:

## 1939-40 NOMINATIONS FOR ELECTIVE OFFICERS

In accordance with provisions of the By-Laws, the Committee on Nominations herewith presents the list of nominees for President-Elect and for the First, Second and Third Vice-Presidents for 1939-40. The election of all nominees shall be by the members of the College at its Annual Business Meeting. Nominations may also be made from the floor at the Annual Business Meeting.

Dr. O. H. Perry Pepper, President-Elect, Philadelphia, Pa., will accede to the Presidency.

*New Nominations*

President-Elect .....	James D. Bruce, Ann Arbor, Mich.
First Vice-President .....	Allen A. Jones, Buffalo, N. Y.
Second Vice-President .....	Gerald B. Webb, Colorado Springs, Colo.
Third Vice-President .....	J. Morrison Hutcheson, Richmond, Va.

Respectfully submitted,

D. SCLATER LEWIS,  
 HENRY M. THOMAS, JR.,  
 FRED W. WILKERSON,  
 DONALD J. FRICK,  
 JAMES ALEX. MILLER, *Chairman,*  
*Committee on Nominations*

Dr. O. H. Perry Pepper, President-Elect, American College of Physicians.  
 Dr. George P. Muller, President-Elect, American College of Surgeons.

Under the able leadership of Governor Bortz's fifteen special committeemen, about one hundred and seventy Fellows and Associates of the College were present, 68 per cent of all the members in this rather large territory. The Buffet Luncheon gave an opportunity for all members to visit the College Headquarters and spend a social hour or two before the formal program began. Due to the large number in attendance it was necessary to schedule the scientific program and clinics in more commodious quarters, and the Medical Laboratories of the University of Pennsylvania, not far removed from the College Headquarters, were utilized.

Among specially invited guests present were:

Dr. Henry M. Thomas, Jr., College Governor for Maryland;  
 Dr. Lewis B. Flinn, College Governor for Delaware;  
 Dr. Clarence L. Andrews, College Governor for New Jersey;  
 Dr. George H. Meeker, Dean of the Graduate School of Medicine, University of Pennsylvania;  
 Dr. W. A. Pearson, Dean of the Hahnemann Medical College of Philadelphia;  
 Dr. George P. Muller, President-Elect of the American College of Surgeons.

At the dinner meeting Dr. O. H. Perry Pepper, President-Elect of the American College of Physicians, addressed the group on the work and activities of the College.

Dr. George P. Muller outlined the work and activities of the American College of Surgeons.

This sectional meeting, although the first for the members in Eastern Pennsylvania, was probably the largest and among the most successful of the State sectional meetings of College members in the country.

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#### INAUGURATION OF THE ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS

Dr. Noble Wiley Jones, 3rd Vice President of the American College of Physicians, was appointed the official representative of this body at the inauguration of the Royal Australasian College of Physicians at Sydney, Australia, during December. The following letter was received by Dr. William J. Kerr, President of the American College of Physicians, immediately following the inauguration, from Dr. Allan S. Walker, Hon. Secretary:

"On behalf of the President and Council of The Royal Australasian College of Physicians, I wish to express our very sincere thanks to your College for giving us the opportunity of having with us as your representative at our Inaugural Meeting Dr. Noble Wiley Jones.

"Dr. Jones has won for himself the regard and friendship of all those he met in our community. His unaffected charm of personality made him a most welcome guest, and his professional erudition gave distinction to our assemblies. He contributed an address on 'Chronic Infection and Atherosclerosis' to one of our scientific sessions which attracted general interest and which we hope to publish in the Medical Journal of Australia.

"Dr. Jones honoured our College by allowing us to confer upon him an Honorary Fellowship. Dr. H. Morley Fletcher, who was the special representative sent from England by the Royal College of Physicians in London, was made our first Honorary Fellow, and it is with pleasure that I inform you that the signature of Dr. Noble Wiley Jones stands as the second on the list of Honorary Fellows in our Register.

"The presence of one of your Vice-Presidents at our Inaugural Meeting was a happy event: it has served to unite our Colleges in the friendship of a common cause, and it will always be a pleasure for us to welcome any of your members to our midst.

"With greetings from our President and Council,

Yours sincerely,

(Signed) ALLAN S. WALKER,

*Hon. Secretary.*"

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Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., addressed the Schuylkill County Medical Society, at Pottsville, Pa., on January 10, on "Deficiency Diseases."

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Dr. Charles E. Lyght (Associate), Director of the Carleton College Health Service, Northfield, Minnesota, presented the Eighth Annual Report of the Tuberculosis Committee of the American Student Health Association, at the Nineteenth Annual meeting of the Association held in New York City, December 29-30, 1938. The Report summarized the results of a national survey of the work being accomplished in the early diagnosis and treatment of tuberculosis among college and university students. Dr. Lyght is serving his third term as chairman of the Tuberculosis Committee.

Dr. Warren Coleman, F.A.C.P., for a great many years located in New York City, and formerly Professor of Clinical Medicine at the New York University College of Medicine, has accepted the Chair of Professor of Clinical Medicine at the University of Georgia School of Medicine at Augusta, Georgia.

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Dr. J. R. Nakada, F.A.C.P., St. Louis, Mo., was the guest of the Jacksonville County Medical Society at Carbondale, Ill., on December 15, 1938, where he presented a paper entitled, "The Medical Management of Duodenal Ulcer."

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Dr. Zachary Sagal, F.A.C.P., New York City, was recently advanced to Associate Physician at Bellevue Hospital.

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Dr. Priscilla White, F.A.C.P., Boston, Mass., was the guest speaker at the Scientific Meeting of the Allegheny County (Pa.) Medical Society, January 17, 1939, at Pittsburgh, her subject being "Diabetic Children." The entire program was presented by women physicians.

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The Thirty-fifth Annual Congress on Medical Education and Licensure was held at the Palmer House, Chicago, February 13 and 14, 1939. At the second session, the Symposium on the Small Hospital, Dr. Malcolm T. MacEachern, F.A.C.P., Chicago, spoke on the "Organization and Management of the Small Hospital" and Dr. William Henry Walsh, F.A.C.P., Chicago, spoke on "Planning for a Small Hospital." Dr. MacEachern is an Associate Director of the American College of Surgeons, and Dr. Walsh is a consultant specialist on hospitals.

Dr. John H. Musser, F.A.C.P., New Orleans, presided at the third session. Among the speakers at this session was Dr. A. J. Carlson, F.A.C.P., Chicago, whose title was "Tenure of Members of the Faculty in Schools of Medicine."

The Federation of State Medical Boards was addressed at its Dinner Meeting by Dr. Willard C. Rappleye, F.A.C.P., Dean of Columbia University College of Physicians and Surgeons, New York, on "Recent Impressions of British Medical Education."

At a subsequent meeting of the Federation Dr. Harold Rypins, F.A.C.P., Secretary, New York State Board of Medical Examiners, Albany, and Dr. Fred E. Clow, F.A.C.P., Secretary, New Hampshire Board of Registration in Medicine, Wolfeboro, delivered addresses on "American Graduates of British Medical Schools" and the "Legal Status of the Intern," respectively.

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Dr. Samuel Goldberg, F.A.C.P., Clinical Professor of Pediatrics at Temple University School of Medicine and Senior Attending Pediatrician to the Jewish Hospital, Philadelphia, was recently elected President of the Philadelphia Pediatric Society.

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Dr. Hyman I. Goldstein (Associate), Camden, N. J., is President of the Northern Medical Association of Philadelphia (founded in 1846). Dr. A. C. Morgan, F.A.C.P., Dr. J. M. Cahan, F.A.C.P., Dr. William A. Swalm, F.A.C.P., Dr. Mitchell Bernstein, F.A.C.P., and Dr. Nathan Blumberg, F.A.C.P., all of Philadelphia, are among the members of the Executive Committee. At the January meeting of this Association Dr. E. J. G. Beardsley, F.A.C.P., and Dr. Goldstein participated in the Scientific Program. Dr. Foster Kennedy, Professor of Neurology at Cornell Medical School, New York City, addressed the Association on February 20, 1939, on "The Organic Basis of the Mind." The discussion was opened by Dr. A. M. Ornstein, F.A.C.P., Assistant Professor of Neurology, University of Pennsylvania School of Medicine.

Dr. David Riesman, F.A.C.P., Professor of the History of Medicine, University of Pennsylvania School of Medicine, has been appointed Honorary Chairman of the Centennial Committee of the Association.

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### OBITUARIES

James Joseph McGuire, 122 West State Street, Trenton, N. J., died at his home October 11, 1938, of arteriosclerosis and nephritis with uremia, at the age of 62.

Dr. McGuire, the son of Felix and Mary Campbell McGuire, was born in Trenton, N. J., May 22, 1876. His father had been engaged in the coal business for many years.

He began his education in the St. John's School in Trenton and entered the St. Joseph College in Philadelphia following that from which he graduated with a B.A. Degree. In 1900, he graduated from the University of Pennsylvania as an M.D.

Following his graduation in medicine, he became an intern in the St. Francis Hospital in Trenton and after one year in that capacity, he began the practice of medicine first on South Broad Street near Center and finally to 122 West State where he was practicing when he died. Together with Dr. G. N. J. Sommer, he led the movement toward this area which is now known as "Medical Row."

In his college days, he was a great baseball player. At Pennsylvania he played in the outfield on the Red and Blue varsity team as well as being a member of the D. J. Wallace baseball club of South Trenton in 1891.

Dr. McGuire was Pediatrician at the St. Francis Hospital, Trenton; consulting Physician, Children's Contagious Diseases Hospital, Trenton; Visiting Physician, Orthopedic Hospital, Trenton, and served for many years on the State Board of Medical Examiners.

He was first appointed to the Board in 1915; served as President from 1921 to 1932 and was Secretary to the Board at the time of his death.

He was a member of the Mercer County Medical Society; the Philadelphia Pediatric Society, Philadelphia Medical Club, the American Medical Association, and a Fellow of the American College of Physicians since 1929.

Aside from his medical interests he was a member of the Knights of Columbus, Catholic Club and the Trenton Country Club. During the World's War, he was a member of the Trenton Draft Board.

Dr. McGuire is survived by his widow, the former Blanche M. Gallagher of Jersey City, N. J.; two daughters, Blanche and Eleanor; a sister, Miss Mary McGuire and two brothers, Timothy and Francis McGuire.

In such a brief span of life he accomplished a great deal. Few knew about his grave illness; it came as a great shock to his friends, and both society and the profession have incurred a great loss.

CLARENCE L. ANDREWS, M.D., F.A.C.P.,  
Governor for New Jersey.

## DR. FREDERICK J. KALTEYER

Dr. Frederick J. Kalteyer, Clinical Professor of Medicine at Jefferson Medical College, died December 21, 1938, at his home 1707 Spruce Street, Philadelphia, of coronary disease.

Dr. Kalteyer was a Texan by birth. He was graduated from the University of Pennsylvania in 1895 and from Jefferson Medical College in 1899. In 1905 he was elected to the Staff at Jefferson and continued that association up until the time of his death.

Dr. Kalteyer was on the staff of the Philadelphia General Hospital, Consultant-physician to the Delaware County Hospital, and was a member of the University and Merion Cricket Clubs.

In 1923 he was elected an Associate of the American College of Physicians.

From time to time he has contributed to the medical literature.

He is survived by his wife and two sisters.

EDWARD L. BORTZ, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania.

## DR. HENRY WOOLFE BERG

Henry Woolfe Berg, A.B., M.D., F.A.C.P., of 10 East 73 Street, New York City, died December 22, 1938, at the age of eighty.

He was born in Austria on Christmas Day, 1858, and was brought to New York City at the age of three years. He was educated in the public schools of New York City and was an honor student at City College, class of 1878. He entered the College of Physicians and Surgeons of Columbia University, receiving his medical degree in 1881. He then became an assistant to Dr. E. C. Sequin, professor of neurology at Columbia, and was also the attending surgeon at the New York Orthopedic Hospital.

In 1883 he became attending physician at the Willard Parker and Riverside Hospitals and was secretary of their joint board for almost thirty years. During the war he directed the care of soldiers and sailors at the Riverside Hospital during an epidemic of cerebro-spinal meningitis. He was also the author of many papers on serum therapy. His connections with the Willard Parker Hospital covered forty-four years, he being Consulting Physician of this institution at the time of his death. In 1899 he was made adjunct physician at Mt. Sinai Hospital and then associate attending physician. In 1923 he was appointed physician of the isolation service there and retained that post until his death.

Dr. Berg was active in other fields. He gave much time to the study of the Board of Education budget and for twenty years frequently appeared in the interest of taxpayers before the Board of Estimate. He also testified before congressional committees on economic matters and several times received a vote of thanks from the Senate Committees, especially for his



help on immigration laws. In his later years Dr. Berg acquired a collection of rare books in which he took a great interest.

Dr. Berg became a Fellow of the American College of Physicians in 1920 and maintained an uninterrupted and active interest to the end of his life. Although advanced in years he was a regular subscriber to the College journal, the Annals of Internal Medicine.

Dr. Berg was survived by two brothers, Abraham Berg and Dr. Albert A. Berg and by two sisters, Mrs. Samuel D. Levy and Mrs. Delia Warschauer.

C. F. TENNEY, M.D., F.A.C.P.,  
Governor for Eastern New York.

## ANOTHER FEATURE FOR THE POST-CONVENTION TOUR TO MEXICO CITY

Lieutenant Colonel Coleridge L. Beaven, M.C., until recently the Commandant of the School of Aviation Medicine at Randolph Field, Texas, one of our Fellows, has invited the members of the Mexico City Post Convention party to visit the School during the stay in San Antonio. Arrangements are now being worked out to make this possible, and it will be one of the high-lights of our short stop in San Antonio. Lieutenant Colonel Fabian L. Pratt, who has succeeded Lieutenant Colonel Beaven as Commandant of the School of Aviation Medicine, and Lieutenant Colonel N. C. Mashburn, the Assistant Commandant, will receive the party on its arrival at San Antonio.



Air Corps Training Center Headquarters, Randolph Field, Texas.

The School of Aviation Medicine had its origin during the World War as the Medical Research Laboratory located at Hazelhurst Field, Mineola, Long Island, N. Y. In 1919 the School for Flight Surgeons was added and the first class graduated. That same year the school was moved to Mitchel Field and in 1922 the name was changed to The School of Aviation Medicine. In 1931 the school was moved to its present location at the Air Corps Training Centre which affords a splendid opportunity for the teaching of aviation medicine from a practical standpoint.

To the excellent clinical facilities offered for teaching by Army, State and City hospitals adjacent to Randolph Field, there are the three classes of flying trainees entering the Training Center annually, numbering around

1,000. These highly selected young men, ranging in age from 21 to 27, are in the pink of physical condition to begin with and are kept so by living in an ideal as well as controlled hygienic environment. This group serves as excellent material for clinical work as well as for the investigation and solution of the many problems connected with aviation medicine.

In addition to the privilege of using these trainees for working out various laboratory experiments, the medical students have the opportunity to observe their progress on the flying line and to see first hand just what type does well in flying training and what type does not. They study the "daily flying log books" and learn from the comments of the flying instructors just why it is impossible to teach certain types of individuals to fly military airplanes.

Since learning to fly is complicated and flight surgeons are expected to select young men who will do well in the job of learning to fly, it becomes necessary for him to know as much about flying as possible. This can be accomplished best by having the Flight Surgeon work at the job of learning to fly. All students at the School of Aviation Medicine are given ten hours flying training. In this training the medical student goes through the same routine as flying students and gains first hand information about the problems of learning to fly.

There are other features on which we are now working that will prove very delightful and which will be announced later.

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## DIABETIC COMA

(AN INVESTIGATION OF MORTALITIES AND REPORT OF A  
SEVERITY INDEX FOR COMPARATIVE STUDIES)\*

By I. M. RABINOWITCH, F.A.C.P., A. F. FOWLER and E. H. BENSLEY,  
*Montreal, Canada*

RECENTLY we<sup>1</sup> reported a method for the treatment of diabetic coma with one simultaneous injection of unmodified and protamine zinc insulin. With this method, it was shown that the blood sugar was rapidly reduced to the normal level, regardless of the degree of hyperglycemia and kept at that level for at least 40 hours, in spite of administration of many hundred (780 to 1020) grams of carbohydrate. In two cases the blood sugars were still normal at the end of 60 hours. That these large amounts of carbohydrates administered were not stored in the tissues artificially, but were utilized either by oxidation or storage or both, was shown in each case by the perfectly normal blood sugar at the end of the period of observation. Also proof that these enormous amounts of sugar were properly utilized were (a) the rapid disappearance of the ketone bodies from the urine, (b) the rapid disappearance of the acetone odor from the breath, and (c) the rapid recovery clinically. As is well known, acetone can, as a rule, be detected in the breath 24 hours or more after return of consciousness. Our past records also show that "the patient is now out of coma but is exhausted" was a common finding; whereas, with this new method, the comfort of the patient was one of the most striking clinical findings. Since then, 14 other cases † have been treated similarly with essentially the same results. A complete report of our experiences to date is now in preparation.

In view of the above-mentioned experiences, an attempt was made to compare the results of this new method with those of other clinics with use of unmodified insulin only. As will presently be shown, however, proper comparison was not possible because of (a) different clinical criteria of

\* Received for publication December 27, 1938.

From the Department of Metabolism, The Montreal General Hospital, Montreal, Canada.

† A number of others were also treated with protamine zinc insulin, but not by the method described.

coma, (b) different laboratory criteria and (c) failure to record all of the variables—duration of the coma, associated condition, etc.—which are known to influence the mortality. That much may, as yet, be done for diabetic coma, and in fact for diabetes in general, is obvious from mortality and morbidity experiences.

It may be stated definitely that, though much progress has been made, the control of diabetes is not as satisfactory as presently available methods permit. From published data<sup>2</sup> it may be calculated that the average ratio of actual to expected deaths \* during the years 1926 to 1928 was, approximately, 250 per cent of the normal. Since then, no data have been published from which such ratios may be calculated. That the number of deaths among large diabetic populations, in general, is, however, still much higher than presently available methods justify, is suggested from the increasing death rate which cannot be accounted for entirely by the increase of population of individuals approaching and past middle life among whom the majority of diabetics originate. That the above-mentioned ratio of actual to expected deaths was too high even in the years 1926 to 1928 is clearly seen in chart 1 in which are graphically recorded the ratios in the Clinic for Diabetes at The Montreal General Hospital before and since insulin. It will be noted that, whereas the ratio was approximately 660 per cent of the normal before insulin, since 1926, it has ranged between 100 and 120 per cent only of the normal. This applied to the diabetics in this Clinic as a whole, that is, to those who attended the clinic regularly and those who were admitted to the clinic for adjustment of the diabetes, but were subsequently referred to their own physicians. The importance of this observation will be seen presently.

Also proof that the control of diabetes is not as satisfactory as presently-available methods permit is the high incidence of coma and its high mortality. Since insulin became available, there have been less than 200 cases of coma among the total diabetic population of this Clinic—that is, among those directly under our supervision and those who had attended the Clinic at the beginning of treatment but who were subsequently referred to their own physicians. The mortality in the whole group was such that coma accounted for 4.5 per cent only of the deaths from all causes; and it will be shown that the coma was precipitated by complications (infection, etc.) in about 80 per cent of the cases; that is, about 20 per cent only were due to dietary irregularities or failure to follow instructions with respect to insulin. That this has not been the experience among large diabetic populations in general is obvious from published reports. In one clinic, for example,<sup>3</sup> approximately two and one-half times the size of our own, coma accounted

\*It is the ratio of the actual to expected deaths which gives a clear insight into the effect of any disease on mortality. For example, of 10,000 people alive in the United States at the age of 40 years, 67 only are expected to die before their forty-first birthday. (See U. S. Life Tables—1936.) If we were to find that, of 10,000 diabetics living in the United States at the age of 40 years, 134 failed to reach their forty-first birthday, the death rate would be twice the normal or expected population death rate. That is, the ratio of actual to expected deaths is a *quantitative* expression of mortality.

for 272 deaths between August 7, 1922 and March 13, 1935; 60 of these deaths had occurred since 1930. These numbers, it should be noted, represented *deaths* and not cases. Assuming a mortality of 50 per cent—that treatment was successful in half of the cases only—to which there would un-

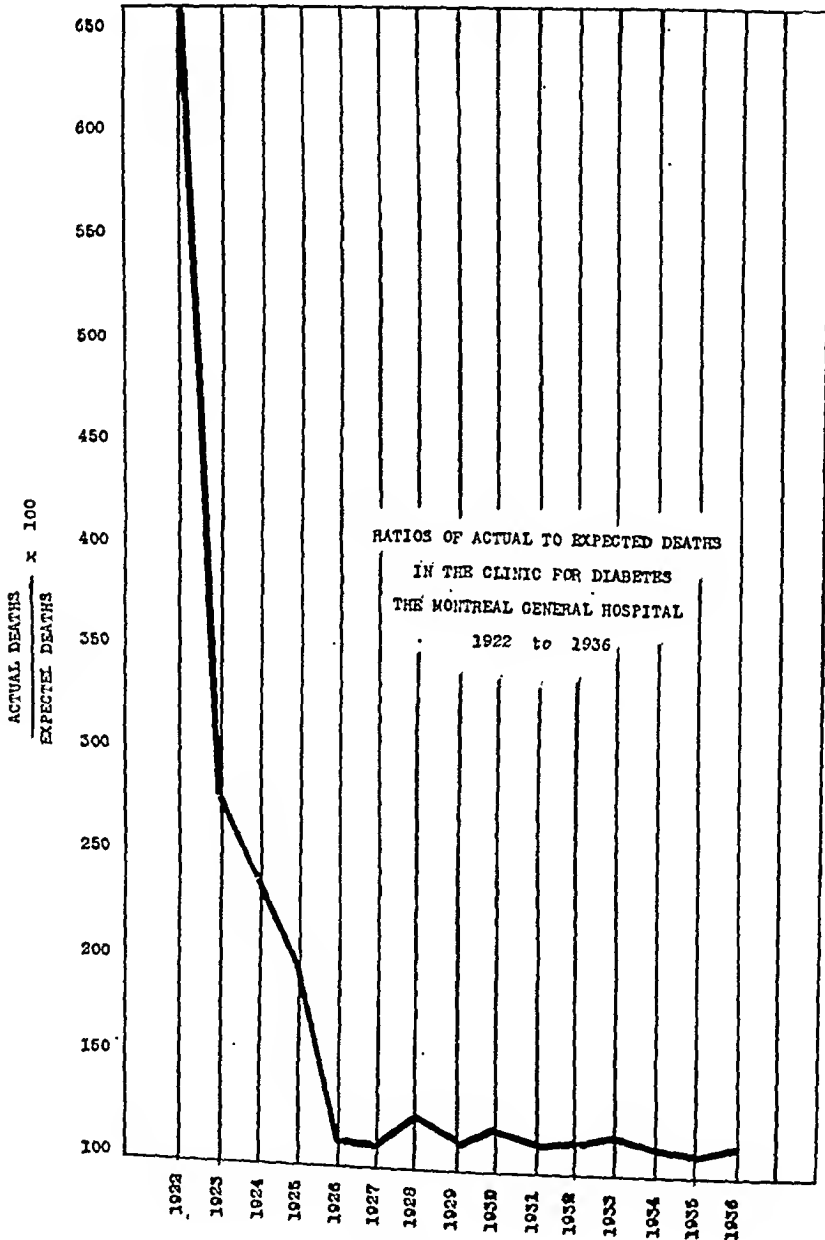


CHART 1.

doubtedly be great objection, there were at least 550 cases of coma among this group of patients during this period. An assumption of a 25 per cent mortality, to which there may be equal objection, would increase the number of cases to over 1000. That this is, approximately, the mortality from coma among large diabetic populations in general is suggested from an

analysis of 1007 cases, cited by 25 different authors.<sup>4</sup> Among these cases, there were 302 deaths—an incidence of 30 per cent. That coma accounts for a very appreciable percentage of deaths from all causes among diabetics is obvious from other data.<sup>5</sup> \*, <sup>6</sup>, <sup>7</sup>, <sup>8</sup>

The deaths among the children are the most disturbing. Diabetic coma is a preventable condition in the vast majority of cases and, when it does occur, it is one of the very few conditions for which there is highly specific therapy—insulin. Also, for a number of reasons (absence of arteriosclerosis, chronic nephritis, etc.) children respond more readily to insulin than adults and, as will be shown, death from uncomplicated diabetic coma is practically inexcusable. In spite of these facts and the presently available methods for the *prevention* of coma, the mortality rate among children, though it has markedly improved since insulin, is still high. Thus, according to a recently published chart<sup>9</sup> the annual death rate from coma was reduced from 45 per 1000 during the period 1922–27 to 5 per 1000 during the period 1932–37. This number of deaths, it should be noted, however, is still very high, when expressed in terms of ratio of actual to expected deaths according to age.<sup>†</sup>

It is important here to observe that, in the interpretation of the mortalities of the above-mentioned clinic, it is necessary to differentiate between the patients directly under the supervision of the clinic and those who had been treated at the clinic but who were subsequently treated elsewhere. Thus, of the 272 deaths from coma, 41 only occurred at the clinic.<sup>11</sup> Of the 69 deaths from coma among the children, 2 only occurred at the clinic.<sup>9</sup>

By dividing the diabetics into those directly under the supervision of clinics and those treated elsewhere, it would appear that proper treatment is possible in clinics only. This, however, is not in accord with our own experiences and the latter we attribute to a large extent to our method of educating diabetics. As will be shown in a separate report<sup>‡</sup> we attribute our satisfactory results to some extent, but not entirely, to our diets. It may be stated that the care with which the diabetic will follow treatment is in direct proportion to the simplicity with which it can be carried out. It is, therefore, necessary here to note that, for over 12 years, our patients have not been taught to use scales to measure their food; for over 10 years they have not been taught carbohydrate, fat, protein and caloric values of food

\* The City of New York has recently shown a marked improvement of mortalities; in 1933, coma accounted for about 35 per cent of all deaths among the diabetics<sup>5</sup>; in 1936, there were 189 deaths only among a total of 2571—an incidence of 7.4 per cent; in 1937, there was a further reduction—coma accounted for 179 cases only among 2669 deaths—an incidence of 6.7 per cent (T. J. Duffield, Registrar of Records, Department of Health, City of New York—personal communication). Among the diabetics of Joslin's clinic, in Boston, from Jan. 1, 1930 to Mar. 13, 1935<sup>3</sup> using the same type of data as our own, that is, patients in the clinic and those treated subsequently elsewhere, coma accounted for 6.1 per cent only of all deaths.

† The ratio of actual to expected deaths among the children in this group of diabetics was higher than these cases of coma indicated, since, in addition to these deaths, there were, excluding two violent causes, 33 from other causes.<sup>10</sup>

‡ In this report, the incidence of ketonuria and change of the lipid content of the blood plasma will be correlated with different variables in the diet—total glucose content, fatty-acid glucose ratio, total protein, biological (protein-sparing) value of the protein, etc.

materials; and, during the last eight years, they have not even been taught urinalysis. We, however, insist upon very careful attention to our unit system of measurement of food materials.

### INTERPRETATION OF MORTALITIES FROM COMA

As stated, interpretation of the different mortalities from coma even in large clinics is very difficult, owing to (a) the different clinical criteria, (b) the different laboratory criteria, and (c) failure to record *all* of the variables which are known to influence the mortality from this condition. That none of the mortalities is strictly comparable with another will be shown in an analysis of the experiences of four clinics, each of which has reported upon no less than 100 cases. It will be shown that the low mortalities do not reflect as successful, nor do the high mortalities reflect as unsuccessful, treatment as they appear to. The clinics, the total number of cases in each clinic and crude (unadjusted) mortalities were as follows:

Clinic	No.	DEATHS	
		No.	%
Joslin <sup>12-18</sup> .....	318	38	11.9
Dillon and Dyer <sup>19</sup> .....	268	167	43.7
Baker (Mayo Clinic) <sup>20</sup> .....	108	17	15.7
The Montreal General Hospital.....	125	33	26.4

### METHOD OF DIAGNOSIS AND MORTALITY

A fundamental principle of statistics is to compare things which are comparable. It is, therefore, necessary to consider, firstly, the different clinical and laboratory criteria used in these clinics for the diagnosis of diabetic coma.

Diabetic coma is a definite clinical entity. The change from the normal state to that of complete coma is, however, as a rule, gradual and the mortality in general varies accordingly. The following is, therefore, the terminology employed in the Clinic for Diabetes at The Montreal General Hospital:

KETOSIS:	Ketone bodies in the urine,* but a normal CO <sub>2</sub> combining power of the plasma.
ACIDOSIS:	Ketone bodies in the urine and reduction of the CO <sub>2</sub> combining power of the plasma, but no clinical signs or symptoms suggestive of coma (vomiting, abdominal pains, Kussmaul respirations, etc.).

\* There are a number of reports of diabetic coma without ketone bodies in the urine.<sup>4, 20, 21, 22, 23, 24</sup> In most cases, the absence of these bodies was apparently due to renal failure, since acetone was found in the breath, blood or cerebro-spinal fluid. Renal failure does not, however, explain *all* of the cases.<sup>22, 23</sup> Other organic acids have been suggested as the exciting agents and for this there appears to be some experimental basis.<sup>25, 26</sup> We have, however, not as yet met with any such cases in this Clinic; the ferric chloride reaction was negative in four cases, but the sodium nitroprusside test was positive and, in each case, there was an acetone odor to the breath.



**THREATENING COMA:** Ketone bodies in the urine, reduction of the  $\text{CO}_2$  combining power of the plasma, clinical signs suggestive of coma (Kussmaul respirations, vomiting, *but no drowsiness—the patient is quite conscious*).

**COMA:** The signs of threatening coma plus drowsiness or a greater degree of unconsciousness. Thus:

- Stage 1: Drowsy
- 2: Semi-conscious
- 3: Unconscious but responds to pain \*
- 4: Completely unconscious

The reliability of this division of coma into four stages may be seen in our mortality experiences shown in table 1. The data require no comment.

TABLE I

Showing Relationship between the Degree of Unconsciousness and Mortality in Diabetic Coma

Stage	Mental state	Number of cases *	Deaths	
			No.	%
1	Drowsy	60	8	13.3
2	Semi-conscious	37	6	16.2
3	Unconscious but response to pain †	13	7	53.8
4	Completely unconscious	11	11	100.0

\* Four cases are omitted—descriptions not sufficiently specific for classification.

† Elicited by touching conjunctivae.

It will be noted that none of our 125 patients was in a state of "acidosis" only; nor were any in a state of "threatening coma" only. Cases of threatening coma might reasonably have been included. Had they not been treated, they would have undoubtedly developed coma and died. By including them, however, the resultant low mortality, though interesting, would not be instructive; *it would afford no indication of the difficulties of the treatment of actual coma, since all cases of acidosis and threatening coma are expected to recover*, unless there is an associated condition which, per se, can cause death. As Joslin pointed out many years ago<sup>27</sup> in one of his discussions of the measures for acid intoxication ". . . they will usually avail even at a stage when the patient is conscious, but exhibits the labored breathing of diabetic coma." This, it should be noted, was *before* insulin.† With insulin, with greater appreciation of the value of fluids, with better cardiac, vasomotor and respiratory stimulants, the mortality in such cases is now expected to be zero.

In view of these facts and the above-mentioned different mortalities in

\* Elicited by touching conjunctivae.

† The statement was also then made that the measures described were not successful when the  $\text{CO}_2$  in the alveolar air was below 15 vol. per cent; but it was considered more than possible that some of these cases will recover in the future with more intensive treatment. Actually, this was found to be so; later experiences—also before insulin—showed recovery in two cases with alveolar  $\text{CO}_2$  values of 11 and 12 vol. per cent respectively.<sup>28</sup>

these four clinics, it is obviously necessary to determine whether cases of acidosis only or threatening coma only were or were not included in any of the other groups of cases. The necessary information was not available in the paper by Dillon and Dyer<sup>19</sup> nor in that by Baker.<sup>20</sup> According to Dr. Dillon, however, cases of ketosis were not included in their report. It is "practically certain" that cases of acidosis, according to our nomenclature were not included. The list, however, does contain cases of threatening coma. The actual number of such cases is now not known. (Personal communication.) Of Baker's 108 cases, 41 were drowsy, 32 were stuporous and 32 were in deep coma. The mental states in the remaining three cases are now not determinable. (Dr. Baker—personal communication.) Analysis of the Boston reports, however,<sup>14-18</sup> showed that they contain a very appreciable number of cases of acidosis and threatening coma; in all there were 118 such individuals, 24 of whom were not only "conscious," but had normal respirations. The reason they were included will be given in the discussion of the CO<sub>2</sub> combining power of the blood plasma. That these were cases of impending coma only was suggested from the extremely low mortality; among these 118 cases, there were 4 deaths only—an incidence of 3.4 per cent—fitting in with the above-mentioned observation that none of such individuals is expected to die, unless the complication can, per se, cause death. Proof that it is necessary to exclude these 118 cases in order that the mortalities of the above-mentioned four different clinics may be strictly comparable was found in the following experiences with (a) the different ages of these patients, (b) the kidney function data, and (c) blood sugar data.

In general, age has a very appreciable effect upon mortality. This is clearly shown in table 2 in which are briefly summarized the experiences

TABLE II  
Showing Relationship between Age and Mortality in Diabetic Coma (819 Cases)

Age Period	Number of Cases	Deaths	
		No.	%
-20	293	15	5.1
21-30	120	20	16.7
31-40	105	24	22.9
41-50	117	43	36.8
51+	184	103	56.0

with the 819 cases in the above-mentioned clinics. In view of these findings, all of the cases in the Boston clinic were divided into two groups, namely, (a) those who from the data in general were suspected to have been cases of impending coma only, and (b) those which were regarded as actual coma and, therefore, comparable with the cases of the other clinics. It is obvious

that if these 118 cases were cases of actual coma, they should, in general, show approximately the same relationship between age and mortality as shown in table 2. The results of this division of cases are shown in table 3.

TABLE III

Showing Relationship between Age and Mortality in Cases of Impending (?) and Actual Coma

Age Period	Impending (?) Coma			Actual Coma		
	Number of cases	Deaths		Number of cases	Deaths	
		No.	%		No.	%
-20	63	0	0	88	3	3.4
21-30	17	0	0	21	4	19.0
31-40	14	1	7.1	26	3	11.5
41-50	13	0	0	28	7	25.0
51+	11	3	27.3	37	17	45.9

It will be noted that, whereas the cases regarded as comparable with the group as a whole (table 2) showed a definite relationship between age and mortality, those suspected of having been cases of impending coma only showed no such relationship.

The possibility that we may have "selected against" very mild, but actual cases of coma was tested by determining the relationship between age and mortality in our very mild, but actual, cases of coma. The results of this investigation are shown in table 4. It will be noted that, *in spite of the*

TABLE IV

Showing Relationship between Age and Mortality in Cases of Diabetic Coma with Drowsiness Only

Age Period	Number of Cases	Deaths	
		No.	%
0-20	24	1	4.2
21-30	6	0	0
31-40	7	1	14.3
41-50	6	1	16.7
51+	17	5	29.4

*mildness of the coma*, a definite relationship was still noted between age and mortality. The relationship between age and mortality will be referred to again.

In table 5 is shown the relationship noted between mortality and the degree of impairment of kidney function, judging from the concentration of urea in the blood. It will be noted that, though the mortalities were

TABLE V

Showing Relationship between Concentration of Urea in the Blood and Mortality in Diabetic Coma

Blood Urea—N (mg. per 100 c.c.)	Dillon and Dyer			Montreal General Hospital		
	No.	Deaths		No.	Deaths	
		No.	%		No.	%
-20	132	30	22.7	11	1	9.1
21-30	53	26	49.1	17	3	17.6
31-40	16	9	56.2	15	3	20.0
41+	55	42	76.4	18	10	55.5

higher among the cases reported by Dillon and Dyer than among our own group, the data clearly show that renal failure has a marked effect upon the mortality from diabetic coma. The Boston clinic reported their kidney function findings in terms of non-protein nitrogen. The data, however, when grouped in accord with the classes shown in table 5, indicate that the experiences were essentially the same. This is shown in table 6. It is,

TABLE VI

Showing Relationship between Concentration of Non-Protein Nitrogen in the Blood and Mortality in Diabetic Coma

Non-protein nitrogen (mg. per 100 c.c.)	Number of cases	Deaths	
		No.	%
-40	75	6	8.0
41-60	66	6	9.1
61-80	33	10	30.3
81+	11	7	63.6

therefore, important to note that when the cases of the Boston clinic were again divided into (a) those suspected of having been cases of impending coma only, and (b) those with actual coma, a definite relationship was noted between the degree of renal failure and mortality in the latter, but not in the former group. This is shown in table 7.

As with age, the possibility was here also considered that we may have "selected against" very mild but actual cases of coma. This possibility was, therefore, here also tested by determining the relationship between the blood urea nitrogen and mortality in our very mild but actual cases of coma. The results of this investigation are shown in table 8. It will be noted that, whereas no relationship was noted between renal function and mortality in the Boston group of suspected cases (table 7) a definite relationship was noted among our mild but actual cases of coma.

TABLE VII  
Showing Relationship between Degree of Renal Failure and Mortality in Cases of  
Impending (?) and Actual Coma

Non-protein nitrogen (mg. per 100 c.c.)	Impending (?) Coma			Actual Coma		
	Number of cases	Deaths		Number of cases	Deaths	
		No.	%		No.	%
-40	33	2	6.1	42	4	9.5
41-60	17	1	5.9	49	5	10.2
61-80	3	0	0	30	10	33.3
81+	2	0	0	9	7	77.8

TABLE VIII  
Showing Relationship between Concentration of Urea in the Blood and Mortality in Cases  
of Diabetic Coma with Drowsiness Only

Blood urea nitrogen (Range)	Number of cases	Deaths	
		No.	%
-20	8	0	0
21-30	9	0	0
31-40	8	1	12.5
41+	5	3	60.0

Further proof of the necessity of excluding the above-mentioned 118 cases of the Boston clinic, in order that the mortalities of the four different clinics may be strictly comparable, was found in the experiences with the blood sugars.

Judging from the literature, it does not appear to be generally recognized that there is a relationship between the sugar content of the blood and mortality. Bizarre experiences have undoubtedly been met with; the highest value appears to have been 2.06 per cent<sup>29</sup>; recovery was noted with a blood sugar of 1.85 per cent<sup>30</sup> and there were no signs of coma in a case with a blood sugar of 1.5 per cent.<sup>31</sup> In general, however, the mortality increases with the degree of hyperglycemia. Thus, among 57 cases in the literature<sup>11, 17, 19, 29-41</sup> including 14 of our own with blood sugar values of over 1.00 per cent, there were 32 deaths—a mortality of 56.1 per cent. The relationship between the concentration of sugar in the blood and mortality is more clearly shown in table 9 in which are recorded the experiences in three of the four above-mentioned clinics. (The necessary data for the calculation of the experiences in Baker's cases are not recorded.)

In view of these findings, all of the cases in the Boston clinic were again divided into those with actual coma and those which were suspected of hav-

TABLE IX

Showing Relationship between the Concentration of Sugar in the Blood and Mortality in Diabetic Coma

Blood Sugar (%)	Boston Clinic			Dillon and Dyer			M. G. H.		
	Number of cases	Deaths		Number of cases	Deaths		Number of cases	Deaths	
		No.	%		No.	%		No.	%
-0.500	190	13	6.8	164	62	37.8	47	7	14.9
0.501-1.000	114	20	17.5	90	48	53.3	56	15	26.8
1.001+	12	5	41.7	14	7	50.0	8	6	75.0

ing been cases of impending coma only. The results of this division will be noted in table 10. Again, it will be noted that though a definite relationship was found between the blood sugar and mortality among the cases of definite coma, no such relationship was found among the group suspected of having been cases of impending coma only.

TABLE X

Showing Relationship between Concentration of Sugar in the Blood and Mortality in Cases of Impending (?) and Actual Coma

Blood Sugar (%)	Impending (?) Coma			Actual Coma		
	Number of cases	Deaths		Number of cases	Deaths	
		No.	%		No.	%
-0.500	91	4	4.4	99	9	9.1
0.501-1.000	26	0	0	88	20	22.7
1.001+	1	0	0	11	5	45.5

As with age and kidney function, the possibility was here also considered that we may have "selected against" very mild but actual cases of coma. This was, therefore, here also excluded by determining the relationship between the blood sugar and mortality in our very mild but actual cases of coma. The results of this investigation are shown in table 11. It will be noted that, whereas a definite relationship was noted between the blood sugar and mortality, in spite of the mildness of the coma among our cases, no such relationship was found among the cases suspected of having been cases of impending coma only (table 10).

In view of the above findings and the definite relationship between the degree of unconsciousness and mortality shown in table 1, more definite information was sought about the mental states of these 118 patients. We

TABLE XI  
Showing Relationship between Blood Sugar and Mortality in Cases of Diabetic Coma with Drowsiness Only

Blood Sugar (Range)	Number of Cases	Deaths	
		No.	%
-500	26	3	11.5
501+	27	5	18.5

then learned,\* as our statistical analyses suggested, that these were cases of threatening coma only, according to our nomenclature. To quote verbatim, "I think it would be fair to state that 'conscious' in our series means a state of severe acidosis *before* definite drowsiness appears" (Dr. A. Marble). It is obvious, therefore, that these 118 cases must be excluded from the Boston reports, in order that the mortality in this clinic may be strictly comparable with those of the other clinics. In doing so, however, the mortality rate is increased from 11.9 per cent, as reported, to 17 per cent. Thus:

	No.	DEATHS	
		No.	%
Whole group.....	318	38	11.9
Acidosis and threatening coma.....	118	4	3.4
Coma.....	200	34	17.0

This correction, it should be noted, does not include analysis of 52 cases in two of the above reports<sup>12, 13</sup> since the necessary information to exclude cases of acidosis and threatening coma from this group is now not available.

CO<sub>2</sub> COMBINING POWER OF THE BLOOD PLASMA

Another variable which makes it impossible to compare exactly the mortalities of one clinic with those of another is one of the *laboratory* criteria for the diagnosis of diabetic coma, namely, the CO<sub>2</sub> combining power of the blood plasma. As will presently be shown, each clinic made use of a different standard.

At the Boston clinic, *every* case was regarded as one of coma whenever the CO<sub>2</sub> combining power of the blood plasma was 20 volumes per cent or less. To quote verbatim<sup>11</sup>: "For some years it has been our practice to classify any case of diabetic acidosis as one of diabetic coma when the carbon dioxide combining power of the blood plasma is found to be 20 volumes per cent or below. This is admittedly an arbitrary and at times unsatisfactory division of cases, but it has the advantage of affording an accurate way of putting into one group a series of cases for future study and comparison.

\* Grateful acknowledgment is due to Dr. A. Marble for his analysis of these cases.

The figure of 20 volumes per cent has the following basis to commend it: in the pre-insulin days most cases of diabetic acidosis with a  $\text{CO}_2$  of above 20 volumes per cent recovered; those below died.\* Hence, our 'coma' cases include, by and large, those cases which without the aid of insulin would have died."

Though the above-mentioned use of the  $\text{CO}_2$  combining power of the blood plasma undoubtedly has the advantages stated, it has its disadvantages, one of which, as was shown, is that it also includes cases of threatening coma, the mortality from which, as stated, is expected to be practically zero and thus masks the difficulties of treatment of cases of actual coma. Equally important, as will presently be shown, is that such classification *excludes all cases of coma with  $\text{CO}_2$  values greater than 20 volumes per cent*. It is necessary here to refer briefly to the origin of this test.

Twenty years ago, the chemistry of diabetic coma appeared to be very simple. Because of incomplete oxidation of fats, ketone bodies appear in the blood and, during their excretion, they carry with them alkali. This results in depletion of the alkali reserve of the body which, in turn, produces the signs and symptoms noted clinically. The  $\text{CO}_2$  combining power of the blood plasma was then regarded as an exact indication of the degree of depletion of alkali. Shortly after, however,<sup>42</sup> it was shown experimentally that the expected reduction of the bicarbonate content of the blood, judging from the excretion of ketone bodies in the urine, does not always occur. Discrepancies were also noted clinically. It is now a well-known fact that the  $\text{CO}_2$  combining power of the blood plasma does not always parallel the degree of coma. It is not uncommon, for example, to meet with patients who are quite conscious with a  $\text{CO}_2$  of 10 volumes per cent or less. A striking example is that of a person who *walked* into the Boston clinic with a  $\text{CO}_2$  value of 4 volumes per cent only.<sup>11</sup> More important, however, is the fact that *there may be profound unconsciousness with  $\text{CO}_2$  values greater than 20 volumes per cent*. Three of Baker's patients were not merely drowsy but actually unconscious when the  $\text{CO}_2$  combining power of the blood plasma was 28 volumes per cent<sup>20</sup> and it is these cases which are often very difficult to treat and which, as will presently be shown, tend to increase the mortality.

Whether the  $\text{CO}_2$  combining power in a case of coma is or is not lower than 20 volumes per cent depends to a large extent upon the condition which precipitated the coma. When acidosis is the dominant factor, the  $\text{CO}_2$  is usually low. When some associated condition precipitated the coma—infection, etc.—unconsciousness may occur while the  $\text{CO}_2$  is still well above 20 volumes per cent. Recognition of this fact is important from the point

\* It should be noted here that death was not the invariable rule in such cases. This is clearly seen in an analysis of the author's own experiences. Thus, among a group of 15 individuals with impending coma treated successfully by Dr. Joslin *before* the days of insulin, one (No. 1566) had a  $\text{CO}_2$  of 18 volumes per cent and another (No. 2366) had a  $\text{CO}_2$  of 15.9 volumes per cent. The latter patient, it should be noted, also vomited, had *soft eyeballs* and Kussmaul respirations and was stuporous, but could be aroused.<sup>28</sup>



of view of prognosis. That the mortality may be very high in spite of CO<sub>2</sub> values greater than 20 volumes per cent is clearly shown in table 12 in which are recorded the experiences in the above-mentioned four clinics with 713 cases in which the tests were made. It will be noted that the highest

TABLE XII  
Showing Relationship between CO<sub>2</sub> Combining Power of the Blood Plasma and Mortality in 713 Cases of Diabetic Coma \*

Plasma CO <sub>2</sub> (Volumes per cent)	Number of Cases	Deaths	
		No.	%
- 5	42	9	21.4
6-10	107	22	20.6
11-15	225	61	27.1
16-20	192	32	16.7
21-25	100	30	30.0
26+	47	23	48.9

\* Data not available in 106 of the 819 cases.

mortality was found in the cases with CO<sub>2</sub> values *greater* than 25 volumes per cent. Had Baker excluded his 34 cases because the CO<sub>2</sub> combining power was greater than 20 volumes per cent, he would have omitted six deaths and there is no doubt that these people died of diabetic coma. Of the 268 cases reported by Dillon and Dyer<sup>19</sup> 109 (!)—an incidence of 40.7 per cent—showed similarly high, and in some cases higher, values. Had Dillon and Dyer excluded all of these cases because the CO<sub>2</sub> combining power was greater than 20 volumes per cent, they would have omitted 47 deaths and there is equally no doubt, as in Baker's cases, that all of these patients were in and died of coma. It will be noted, in the group as a whole, that of these 713 cases, 147—an incidence of 20.6 per cent—had CO<sub>2</sub> values greater than 20 volumes per cent and among them there were 53 deaths—a mortality of 36.1 per cent. To include all of his cases of coma, Baker had to raise the diagnostic level of the CO<sub>2</sub> to 25 volumes per cent. Dillon and Dyer had to increase it to 29 volumes per cent. Others had to increase it to a still higher level. Hartmann's juvenile diabetics are an example.<sup>43</sup> That there have been cases of coma at the Boston clinic with CO<sub>2</sub> values greater than 20 volumes per cent is clearly shown in one of the reports.<sup>14</sup> To the end of 1929, there were 11 such cases; but, to quote verbatim, though "strictly coma," they were excluded because of CO<sub>2</sub> values greater than 20 volumes per cent. Among them, there were no deaths.<sup>15</sup> Because of their exclusion, it is obvious that the mortality in the Boston clinic was *lower* than reported. It is, however, equally obvious that, because of their exclusion, exact comparison of mortalities is not possible. The number of cases which have been excluded during the last 10 years are now not known,

since they were not classified under coma. (Dr. A. Marble—personal communication.)

Aside from all of the above-mentioned factors which make it impossible to evaluate the mortalities of these clinics, there are, as will presently be shown, a number of other and very important variables to consider. It will be necessary here to refer again to age and kidney function.

### AGE AND MORTALITY

"Youth carries with it a great advantage."<sup>11</sup> Of this there is no doubt. As stated, among children, excluding complications which may, per se, cause death or interfere with the action of insulin, the mortality is expected to be very low. Thus, in Baker's group of cases, the mortality in the first four decades was 4.2 per cent; whereas, in the next four decades it was 37.8 per cent. In the comparison of the mortalities of the different clinics, it is, therefore, obviously necessary to take into consideration the percentages of children. It is also necessary to determine whether the adults are strictly comparable, since age is here also a factor. In table 13 are,

TABLE XIII

Showing Relationship between Mortality and Maximum, Minimum and Average Ages and Percentage of Children in 701 Cases of Diabetic Coma

Clinic	Ages			Ratio of children to adults			Total Mortality (%)
	Maximum	Minimum	Average	Total number	Children		
					No.	%	
Dillon and Dyer.....	83	4	37.8	268	30	11.2	43.7
M. G. H.....	76	2	34.9	125	26	20.8	26.4
Boston.....	72	2	30.5	200*	57	28.5	17.0†
Baker.....	74	3	31.2	108	32	29.6	15.7

\* Does not include 118 cases of impending coma. Including the cases of impending coma, the maximum, minimum and average ages were 72, 2 and 28.7 years respectively and children accounted for 31.4 per cent of the total group—100 children among 318 cases.

† Including the cases of impending coma, the total mortality was 11.9 per cent. See text.

therefore, shown (a) the maximum, minimum and average ages of the patients and (b) the percentage of children in each of these four clinics. From the maximum and minimum ages only, it would appear that the experiences of these four clinics were practically the same. The averages, however, show that the Boston patients\* and those in Baker's group were younger than our own and that Dillon and Dyer had still older ages to contend with. The differences are not marked. It is, however, important to note that children accounted for a definitely higher percentage of cases

\* The average age of the group as a whole in the Boston clinic was 28.7 years. The figure 30.5 years is the result of excluding the cases of threatening coma.

in the Boston\* and Baker groups than in our own and in those of Dillon and Dyer. A priori, therefore, the lowest mortality would be expected among the two former groups. This, as will be shown, accounts to some extent, but not entirely, for the different mortalities.

### KIDNEY FUNCTION AND MORTALITY

Failure of kidney function is a serious complication of diabetic coma (tables 5 and 6). Albuminuria is, per se, of very limited significance; it is found almost invariably. Retention of waste products in the blood, however, as a rule indicates that the coma is at least of 24 hours' duration and, as will be shown (table 18) the mortality increases with the duration of the coma. In such cases, the patient may recover from the coma completely and then become uremic. Such individuals, as one of us<sup>44</sup> has shown, do not always die. As a rule, however, there is a remarkable parallelism between the concentration of urea in the blood and mortality. Of the six cases reported by Fullerton, Lyall and Davidson<sup>45</sup> with urea nitrogen values greater than 50 mg. per 100 c.c., four died; whereas, among 13 cases with lower values, there was one death only. Tables 5 and 6 show the same relationship between renal failure and mortality in a much larger group of cases. In the interpretation of the different mortalities of these clinics, it is, therefore, obviously necessary to determine the percentages of individuals with, and without, impairment of kidney function in each clinic. In the calculations, the following were taken as the upper limits of normality:

Urea nitrogen .....	20	mg. per 100 c.c. blood
Non-protein nitrogen .....	40	" " " " "

A summary of the findings is shown in table 14. It will be noted that the average severity of the coma in our cases was such that 18 per cent only escaped sufficient damage to cause urea retention. According to the percentage of cases with renal failure, the highest mortality was, therefore, to be expected among our own cases. Actually, it will be noted (table 14) this was not so. There are, however, still other variables to consider.

### COMPLICATIONS AND MORTALITY

The influence of a given complication upon the course of the coma in any given case is very difficult to estimate, even with a large experience and laboratory aids. Evaluation of cases in the literature is still more difficult. Infection is an example. It may not only precipitate coma by inhibiting the action of the endogenous, but as was shown by one of the writers (I.M.R.), it may with or without fever, completely inhibit the action of exogenous insulin as well.<sup>46, 47</sup> The effects of complications are not predictable; for example, there may be no difficulty whatever even with the

\* In a publication from this clinic<sup>18</sup> it is stated there were 134 children. Analysis of the data, however, show there were 100 only of 15 years of age and under. The remainder were children at the time of the discovery of the diabetes, but not at the time of the coma. Of these 100 cases, 43 were cases of impending coma.

TABLE XIV

Showing Relationship between Mortality and Percentage of Cases with Normal Kidney Function According to Urea Nitrogen and Non-Protein Nitrogen Concentrations in the Blood in 501 Cases of Diabetic Coma \*

Group of Cases	Number of Patients	Normal Kidney Function †		Total Mortality (%)
		No.	%	
M. G. H.....	61	11	18.0	26.4
Boston.....	130	42	32.3†	17.0§
Baker.....	54	27	50.0	15.7
Dillon and Dyer.....	256	132	51.5	43.7

\* Data not available in 200 of the 701 cases of actual coma.

† Urea nitrogen less than 20 mg. or non-protein nitrogen less than 40 mg., per 100 c.c. blood.

‡ In the whole group (impending and actual coma) among 185 cases, the kidney function was normal in 75—an incidence of 40.5 per cent.

§ Does not include cases of impending coma. Including such cases, the total mortality was 11.9 per cent. See text.

TABLE XV

Showing Influence of Complications upon Mortality in 767 Cases of Impending and Actual Coma \*

Clinic	No Complications			Complications		
	Number of cases	Deaths		Number of cases	Deaths	
		No.	%		No.	%
Mer.....	44	2	4.5	64	15	23.4
Boston †.....	208	9	4.3	58	20	34.5
Dillon and Dyer.....	129	32	24.8	139	85	61.2
M. G. H.....	25	2	8.0	100	31	31.0
Total.....	406	45	11.1	361	151	41.8

\* Data not available in 52 of the 819 cases.

† Data with respect to complications available in 266 of the 318 cases of impending and actual coma. Necessary data to separate impending from actual coma with respect to complications not available.

severest forms of infection.\* In general, however, complications have a marked effect upon mortality. This is clearly shown in table 15 in which are briefly summarized the experiences with 767 of the above-mentioned cases in which the necessary data were available.† It will be noted that the

\* The most striking reduction of the blood sugar with our new method of treating coma was noted in a case of a man, aged 54 years, with bilateral otitis media, bilateral pneumonia, bilateral phlebitis and a decubitus ulcer. The blood sugar, in this case, was reduced from 1.110 to 0.196 per cent in 10 hours (Hosp. No. 890/38).

† Exact separation of the complicated from the uncomplicated cases in the Boston clinic was not possible because of insufficient data. It will be noted that, of the 318 cases, the necessary information was available in 266 only. That the percentages calculated approximate the conditions very closely is suggested from a recent statement. "In the last 100 consecutive cases of coma it seemed definite that in 50 the cause was breaking of diet, too little or no insulin, or both. There were 13 other cases in which the cause was not apparent, but we suspect that in most of them it was diet-breaking or inadequate insulin dosage. In the same series of 100 cases there were 19 in which infections probably played a large part in causing the acidosis." 11

average mortality with complications was approximately four times greater than that without complications.\* It is obvious, therefore, that in order to interpret the different mortalities of these clinics, consideration must also be given the percentage of complicated cases in each of these clinics. These are shown in table 16. It will be noted that, according to this variable alone,

TABLE XVI

Showing Relationship between Total Mortality and Percentage of Cases with Complications (767 \* Cases)

Clinic	Number of Cases	Total Mortality (%)	Cases with Complications	
			No.	%
Boston .....	266	11.9†	58	21.8
Dillon and Dyer .....	268	43.7	139	51.9
Baker .....	108	15.7	64	59.2
M. G. H. ....	125	26.4	100	80.0

\* Data not available in 52 of the 819 cases.

† Includes cases of impending and actual coma. Necessary data to separate impending from actual coma with respect to complications not available.

the highest mortality was expected among our cases. Actually this was not so.

For many years, we have taught our students at McGill University that death from uncomplicated diabetic coma is practically inexcusable. This, we believe, still holds and is clearly shown in table 17; of the 33 deaths

TABLE XVII

Showing Total Number of Deaths and Deaths without Complications

Clinic	Total Deaths	Deaths Without Complications	
		No.	%
M. G. H. ....	33	2	6.1
Baker .....	17	2	11.8
Dillon and Dyer .....	117	32	27.4
Boston .....	38	11	29.0

among our cases, 2 only occurred in cases of uncomplicated coma and one of these patients died within 10 minutes of her admission to the hospital, before any treatment could be given, other than the insertion of the hypo-

\* It is of interest also to note that the experiences in the Boston and Mayo clinics and our own were remarkably alike. The marked difference noted in the group of cases reported by Dillon and Dyer is undoubtedly due to the types of patients these authors had to contend with. It should be noted that, whereas the Boston and Mayo clinics and our own have their quotas of extremely unreliable patients and those who would be reliable but are unable to follow the treatment prescribed, the Philadelphia General Hospital's group of cases consists very largely of the latter type.

dermic needle. The explanation of the high mortality in the group reported by Dillon and Dyer and in the Boston group is not known. There are, however, a number of other variables still to be considered in the interpretation of the mortality from coma.

#### OTHER VARIABLES

*Duration of the Coma and Mortality.* The duration of the coma prior to treatment has a very appreciable effect upon mortality. This is clearly shown by our own experiences and those of Dillon and Dyer. The data are briefly summarized in table 18. The necessary data to adjust the mortalities of the other two clinics because of this variable are, however, not available.

TABLE XVIII  
Showing Relationship between Duration of Diabetic Coma and Mortality

Clinic	Duration of coma	Mortality (%)
Dillon and Dyer.....	Less than 24 hrs.	34.3
	More " " "	51.1
M. G. H.....	Less than 24 hrs.	14.3
	More " " "	28.6

*Degree of Unconsciousness and Mortality.* As shown in table 1, there is a very definite relationship between the degree of unconsciousness and mortality; with drowsiness only, our mortality was 13.3 per cent; with semi-consciousness, it was 16.2 per cent; with unconsciousness, but when there was response to painful stimuli and the eye reflex, the mortality was 53.8 per cent; whereas, with complete unconsciousness, the mortality was 100 per cent. The necessary details to adjust the mortalities of the different clinics because of this variable were, however, not available.

*Blood Pressure and Mortality.* Diabetic coma, when severe and of long duration, generally results in vasomotor collapse. In table 19 are, therefore,

TABLE XIX  
Showing Relationship between Systolic Blood Pressure and Mortality in Diabetic Coma

Systolic blood pressure (mm. Hg)	Mortality (%)
Over 90 mm.	11.5
Under 90 "	53.8

very briefly summarized the relationship noted in our cases between the systolic blood pressure and mortality. It will be noted that the mortality was, approximately, five times as high when the systolic blood pressure was under 90 mm. Hg than when it was above this level. The necessary data

to compare our experiences with those of the other clinics and thus to adjust the mortalities according to this variable also were not available.

*Blood Sugar and Mortality.* It was shown that the mortality of diabetic coma is influenced to some extent by the height of the blood sugar (tables 9 and 10). The blood sugar data of three only of the four clinics were available. Adjustment of the mortalities on this basis, however, does not appear to be necessary, since the blood sugars of over 1.000 per cent accounted, approximately, for the same percentage of cases in each group. Thus:

Clinic	Blood sugars greater than 1.000 per cent
Boston.....	5.6 per cent
Dillon and Dyer.....	5.2 " "
M.G.H.....	7.2 " "

*Leukocytosis and Mortality.* The cause of leukocytosis in diabetic coma is not known. It may, however, be further increased by conditions which, per se, can result in an increase of the white cell content of the blood—infection, etc. Dillon and Dyer<sup>19</sup> found no relationship between their mortality and the degree of leukocytosis. Statistically, however, according to our data, there appears to be some relationship. This is shown in table 20. It is of interest to note that when the cases were divided into three

TABLE XX

Showing Relationship between Degree of Leukocytosis and Mortality in Diabetic Coma

	Mortality (Per cent)		
	Whole group	With infection	Without infection
—25,000	17.0	17.9	12.5
25,001–50,000	15.8	13.3	25.0
50,001+	33.3	33.3	No cases

large groups and then into (a) those with infection and (b) those without infection, no cases without infection were found with cell counts of over 50,000.

*Other Factors.* Adjustment of the mortalities of these clinics was complicated by a number of other variables. Every clinic, for example, has its deaths which are not chargeable to any form of treatment. These include the deaths which occur within a few minutes after admission of the patient to the hospital before it is possible to institute the necessary measures for circulatory collapse. They also include the deaths resulting from the associated condition (gangrene, etc.) days, weeks and months after *complete*

recovery from the coma. Among our 33 deaths, there were 16 such cases. Excluding such cases which are not chargeable to any form of treatment of coma, our mortality was 13.6 only—17 deaths among 125 cases—in spite of the high average duration of the coma, the high incidence of adults, the high incidences of complications and renal failure. The necessary data to adjust the mortalities in all of these clinics because of this variable were, however, not available.

### SUMMARY

Crude death rates—deaths expressed in percentages of total number of cases without due consideration of the many variables which are known to influence the mortality from coma—though interesting as isolated statements of facts are of very limited significance. They afford no indication of the degree of success with the method used for the treatment of the coma. As was shown, none of the mortalities of the four clinics investigated is, therefore, comparable with that of another; none indicates the degree of success with the treatment used.

The more important factors which must be taken into consideration in the interpretation of mortalities from diabetic coma include (1) the clinical criteria for the diagnosis of coma, (2) the level of the  $\text{CO}_2$  combining power of the blood plasma, (3) age, (4) the duration of the coma, (5) the degree of unconsciousness, (6) the blood pressure, (7) the degree of renal impairment, and (8) the associated conditions or complications other than renal failure which can, per se, cause death. Other, but less definite, variables appear to be the concentration of sugar in the blood and the degree of leukocytosis.

### A QUANTITATIVE INDEX FOR ESTIMATION OF SEVERITY OF COMA IN DIABETES

In view of the above observations, an attempt was made to find a *quantitative* method for the estimation of the degree of severity of the coma in any given case, so that, *in the future*, the mortalities with any given method may be compared with those of another with a reasonable degree of accuracy. Encouragement was found in the experiences of life assurance companies and in medicine in general. As is well known, life assurance companies "rate" their applicants according to a number of generally accepted "impairments"—age, body weight (percentage of excess weight, degree of underweight), occupation, habits, etc.; that is, they evaluate their risk *quantitatively*. Medicine, in general, is also—though very slowly—becoming quantitative. Quantitative determination of the degree of hyperthyroidism from the basal metabolic rate is one example. Quantitative measurement of the degree of control of diabetes<sup>48</sup> is another. That the



Severity Index to be reported here will permit comparison of experiences of one clinic with those of another with a reasonable degree of accuracy and thus afford a means of evaluating different methods of treatment in the future will be shown in a number of ways.

### BASIS OF SEVERITY INDEX

It would require a large number of additional tables to demonstrate the development of the Severity Index to be reported here. For purpose of brevity, these are omitted. Briefly, to each of the above-mentioned variables was assigned a number of values and the latter were correlated with the mortality among our cases of coma. Thus (table 21) since a relationship

TABLE XXI  
Calculation of Severity Index

Factor	Rating				
	1	2	3	4	5
Age (years).....	-15	16-30	31-50	51-70	71+
Duration of coma (hours).....	-12	13-24	25-36	37-48	49+
Degree of unconsciousness.....	Drowsy	Semi-conscious	Unconscious but response to pain *	Completely unconscious	
Coffee ground vomitus.....			Present		
Infection.....			Present		
Blood pressure (systolic).....	89-80	79-70	69-60	59-50	49-
Plasma carbon dioxide combining power.....	19-16	15-12	11- 8	7- 4	3-
Blood urea nitrogen (mg. per 100 c.c.).....	21-30	31-40	41-50	51-60	61+
Associated conditions: †.....	Very mild	Mild	Moderately severe	Severe	Very severe

Clinical Stage	Severity Index
Very mild.....	- 5
Mild.....	6-10
Moderately severe.....	11-15
Severe.....	16-20
Very severe.....	21+

\* Elicited by touching conjunctivae.

† Include only acute conditions capable of causing death independent of the coma.

was found between the duration of the coma and mortality, five different values were assigned to this variable. To a duration of 12 hours or less, the value assigned was one; a duration of 13 to 24 hours was given a value of 2; a duration of 25 to 36 hours was given a value of 3, etc.

It will be noted a number of variables—blood sugar, leukocyte count,

etc.—are not included in this Index. Though a relationship was found between these variables and mortality, they were omitted because the correlation was not sufficiently positive. The data also showed that exceptions could be taken to any of the variables *when used to the exclusion of all others*; none was found to be a reliable index, per se. The CO<sub>2</sub> combining power of the blood plasma was the most striking example of this fact. The *combined* use of all of these variables according to the method shown in table 21, however, resulted in an index of severity far superior to the general clinical impression as a guide. This is clearly shown in tables 22 and 23 in

TABLE XXII

Showing Relationship between Severity Index and Mortality in Diabetic Coma

Severity Index	Number	Deaths	
		No.	%
- 5	2	0	0
6-10	40	2	5.0
11-15	31	6	19.4
16-20	22	11	50.0
21+	6	5	83.3

TABLE XXIII

Showing Relationship between Clinical Impression of Severity and Mortality in Diabetic Coma

Clinical impression	Total Number	Deaths	
		No.	%
Very mild.....	3	0	0
Mild.....	28	4	14.3
Moderately severe.....	32	3	9.4
Severe.....	19	4	21.1
Very severe.....	19	13	68.4

which mortality is correlated with the Severity Index and the clinical impression.

#### CALCULATION OF SEVERITY INDEX

The following three cases are examples to demonstrate the use of the different values assigned to the different variables for the calculation of the Severity Index:

## EXAMPLE 1:

Factor	Rating
Age..... 5 years	1
Duration of coma..... 16 hours	2
Degree of unconsciousness..... Drowsy	1
Coffee ground vomitus..... Absent	0
Infection..... Absent	0
Blood pressure (systolic)..... 110 mm. Hg	0
CO <sub>2</sub> ..... 8 vols. per cent	3
Blood urea nitrogen..... 15 mg. per 100 c.c.	0
Associated condition..... None	0
Severity Index.....	<u>7</u>
Conclusion: Mild	

## EXAMPLE 2:

Factor	Rating
Age..... 35 years	3
Duration of coma..... 20 hours	2
Degree of unconsciousness..... Drowsy	1
Coffee ground vomitus..... Present	3
Infection..... Present	3
Blood pressure (systolic)..... 108 mm. Hg	0
CO <sub>2</sub> ..... 18 vols. per cent	1
Blood urea nitrogen..... 25 mg. per 100 c.c.	1
Associated condition..... Upper respiratory tract infection	0
Severity Index.....	<u>14</u>
Conclusion: Moderately severe	

## EXAMPLE 3:

Factor	Rating
Age..... 56 years	4
Duration of coma..... 30 hours	3
Degree of consciousness..... Semi-conscious	2
Coffee ground vomitus..... Absent	0
Infection..... Present	3
Blood pressure (systolic)..... 55 mm. Hg	4
CO <sub>2</sub> ..... 9 vols. per cent	3
Blood urea nitrogen..... 40 mg. per 100 c.c.	2
Associated condition..... Lobar pneumonia	3
Severity Index.....	<u>24</u>
Conclusion: Very severe	

## SUMMARY

The incidence of diabetic coma is still high, in spite of the presently-available methods for its prevention.

The mortality from diabetic coma still appears to be very high in spite of the presently-available methods for its treatment.

The best indication of the value of any given form of treatment for diabetic coma is the influence of that treatment upon mortality. An attempt was, therefore, made to compare the results of our new method of treatment with the methods presently in use. Analysis of the data, however, showed that none of the mortalities reported by the different clinics investigated is comparable with our own or with those of any other clinic, because of the use of different clinical criteria and different laboratory criteria for diag-

nosis and, also, because of failure to record all of the variables which are known to influence the mortality from coma. It is shown that none of the mortalities reported indicates the degree of success with the treatment employed. The variables which must be considered in the interpretation of mortalities from diabetic coma are discussed.

A quantitative index for estimation of the severity of diabetic coma and thus for evaluation of different methods of treatment in the future is reported.

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# THE CLINICAL SIGNIFICANCE OF PUNCTATE BASOPHILIA IN THE ERYTHROCYTE\*

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THE purpose of this study was to evaluate the clinical significance of punctate basophilia by estimating the number of such cells per million erythrocytes in the blood films of persons with widely varying states of health. The need for some definite standard became apparent from reports, made by an unusually careful laboratory technician, which showed the frequent appearance of punctate basophilia in the routine blood smears of office patients. Also, my interest had been stimulated during the past several years by observations on patients in the hematologic clinic of the University of California, showing punctate basophilia to be present in conditions quite apart from lead absorption and lead intoxication.

Our findings raised the following questions concerning the clinical significance of punctate basophilia, or stippling, as it is frequently termed:

(1) To what extent and how frequently does punctate basophilia occur in apparently normal individuals?

(2) How frequently is it found in the "general run" of office patients, who have no obvious history or findings indicative of lead absorption? Is it present in such patients to a greater degree than in normal individuals?

(3) Can punctate basophiles be considered to any extent specific for lead absorption or lead intoxication?

A search of the literature for an answer to these questions discloses such marked variation of opinion that it is not possible to reach any clear-cut conclusion. Price-Jones<sup>1</sup> maintains that punctate basophilia may occur in healthy persons, that it is always present in embryonic blood, and that it is found in the blood of newborn children and animals. He states that the phenomenon occurs in malaria, pernicious anemia, and secondary anemia from toxic infections (tuberculosis, pneumonia, enteric fever, malignant disease, etc.) He believes that in post-hemorrhagic conditions punctate basophilia occurs less frequently, although in gastric hemorrhage where blood is digested and the products of destruction of blood-cells are absorbed in the system, stippled cells are often found in great numbers. Price-Jones mentions an extreme degree of basophilia found in an alcoholic patient with anemia, due to hematemesis. Nägeli<sup>2</sup> is reported to have found stippling

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in his own red blood cells for 30 days following a meal of black pudding, "Genuss von Blutwurst."

Various authors investigating the occurrence of punctate basophilia in the blood smears of normal subjects have reported conflicting findings. E. W. Brown<sup>3</sup> stated that, using Wright's stain, no evidence of basophilic stippling was found in any of the blood smears from 55 apparently normal persons. Mayers<sup>4</sup> examined blood films from 250 normal persons and found one cell showing punctate basophilia. In this study, a special eosin methylene-blue stain was used, and the films fixed in methyl-alcohol. Kogan and Smirnowa<sup>5</sup> studied individuals not working in lead industries and could find no instance of punctate basophilia except in association with anemia. They likewise fixed films in methyl alcohol and used a methylene-blue stain. Davidson and his associates<sup>6</sup> at Aberdeen University, using Leishman's stain, examined many blood films from patients attending the blood clinic, and found punctate basophilia very rarely except where the degree of anemia was severe. McDonald<sup>7</sup> quotes Duhig as having found stippled cells in 43 per cent of 100 supposedly normal children. Lane<sup>8</sup> found punctate basophilia in approximately 50 per cent of 223 normal controls. Of this group, 65 who were students had counts of from 100 to 1,000 stippled cells per million red cells, and the counts of three were as high as 2,000; 155 manual workers ran higher counts: 21 from 1,000 to 2,000, and three above 2,000 punctate cells per million red cells. Lane calls attention to the desirability of a quantitative standard in estimation of punctate basophilia. W. T. Nelson<sup>9</sup> of Australia, using a "Seidentopf change-over condenser" and dark-field illumination, found stippling of the red blood cells in 85 per cent of a group of "apparently healthy indoor workers." The counts ranged from 100 to 4,400 per million red cells. He studied blood films from another group of civil servants examined for what he terms "various illnesses of an everyday character," and found, in 76 per cent, from 300 to 7,200 stippled cells per million red cells. In addition, he found a high percentage of films positive for punctate basophilia in workers exposed to benzol and its derivatives, and to carbon monoxide, and trinitrotoluene. Nelson used an alkaline methylene-blue stain recommended by Sellers.<sup>10</sup> He believes the dark-field method reveals many red cells with fine granules that are missed by ordinary bright-field illumination. Later, Nelson, Lockwood and Mackay<sup>11</sup> examined a number of naval ratings and trainees. Of this group, 255 men with no history of exposure to lead had an average of 937 stippled cells per million red cells. In a group of 59 men with the history of slight exposure to lead, the average number of stippled cells per million red blood cells was 4,335. In 41 workers in battery factories, the average was 14,220. Twelve of these men with lead poisoning had an average punctate basophile count of 36,382 per million red cells. Trautman<sup>12</sup> and Schmidt<sup>13</sup> found punctate basophilia in the erythrocytes of 21 per cent of 100 healthy individuals.

Observations and studies have been recorded showing stippling of erythrocytes to occur in workmen who have had no obvious exposure to lead. H. Lehmann<sup>14</sup> reported this finding in workmen exposed to cement dust, and confirmed his results with experimental observations on guinea pigs. Lehmann quotes from a report by Konrich<sup>15</sup> who produced punctate basophilia with injections of sand, brown coal and anthracite in very fine emulsion. Mertenskötter,<sup>16</sup> by injecting cement dust into rabbits, was not able to confirm Lehmann's findings of punctate basophilia. Scharlau<sup>17</sup> produced polychromatophilia but not punctate basophilia by the administration of coal, stone and cement dust. Breitburg and his colleagues<sup>18</sup> reported the production of stippling by administration of arsenic; Brüllowa and others<sup>19</sup> by inhalations of benzene. Brocher<sup>20</sup> found punctate basophilia in 90 per cent of printers using benzol in connection with rotogravure work. Engelhardt<sup>21</sup> found punctate basophilia in a large proportion of workers exposed to benzol. Stengel, White and William Pepper,<sup>22</sup> in 1902, studied the blood smears of 105 hospital patients with various diseases. No granules were found in 71 cases. Stippling was found in the smears of 34 patients with the following diagnoses: typhoid fever, 3 cases; valvular heart disease, 3 cases; peritonitis, 3 cases; septicemia, 3 cases; tuberculous arthritis, 2 cases; malaria, 2 cases; pertussis, heart disease and nephritis, lobar pneumonia and pleurisy, phthisis, malignant endocarditis, aneurysm and nephritis, nephritis and anemia, splenic anemia, secondary anemia, pseudoleukemia, chronic diarrhea, phlyctenular conjunctivitis, orchitis, carcinoma of stomach, lymphoma of neck, sarcoma of neck, empyema, osteomyelitis, 1 case each. The authors cite the following experiments: Strauss<sup>23</sup> found punctate basophilia to occur in patients with atropine poisoning, and in rabbits and frogs poisoned with pyrodine. Kammer and Rohnstein<sup>24</sup> found stippling of erythrocytes in the blood of rabbits on the fourteenth day of intoxication with phenylhydrazine. Sabrazes, Bourret and Léger<sup>25</sup> refer to a case of fatal copper poisoning in which numerous cells with punctate basophilia were found. Stengel, White and William Pepper<sup>22</sup> found numerous stippled red blood cells in a dog poisoned with potassium chlorate. These cells were numerous also in the blood of dogs kept for many days under the influence of toxic doses of pyrodine.

Teleky<sup>26</sup> and K. B. Lehmann<sup>27</sup> are not convinced of the specificity of punctate basophilia as indicative of lead poisoning; they believe that this phenomenon is present in other conditions as well.

#### EXPERIMENTAL STUDY

*Material and Technic.* In order to obtain data concerning the clinical significance of punctate basophilia, experimental studies were made on the following groups of persons:



GROUP 1: Blood smears were studied from 205 apparently normal individuals. Brief histories were obtained from all persons in this group, which comprised technicians, medical students, interns and attending physicians at the University of California Medical School. The examinations were performed in the hematologic clinic of the out-patient department.

GROUP 2: From the author's private practice, 234 patients were selected because they showed punctate basophilia in routine blood films taken as part of the diagnostic survey of each patient. Blood smears of 400 patients had been examined over a period of two years. In this group, no special preliminary search for stippling had been made; in each instance it was noted in the routine inspection of the patient's blood film.

GROUP 3: Five patients with polycythemia vera and two with lymphatic leukemia were given lead acetate by mouth, 0.3 gm. in capsules once or twice daily. The patients with polycythemia were under observation to test the efficacy of administration of lead by mouth as a method of reducing the red blood cell and hemoglobin levels; and the patients with lymphatic leukemia were used as controls. Originally, one of the patients with polycythemia vera had been studied to determine the relationship between punctate basophilia and reticulocytes. The blood of patients with polycythemia vera does not, ordinarily, show much change in the reticulocyte level until the red blood cells fall below approximately 5 million, hence they seemed particularly suitable for such a study. The red blood cells in this patient, who unfortunately had severe lead intoxication because of unusual susceptibility, did not rise above 5 million for over one year. For this reason, experimental studies were extended to include other patients with polycythemia vera, and accurate determinations were made of the stippled cell-reticulocyte ratio. Two patients attending the general medical clinic, who showed slight punctate basophilia, were given injections of alkaline hematin, intravenously and intramuscularly.

GROUP 4: Blood films were studied from a group of eight patients working in the plant of a paint-manufacturing company at South San Francisco; also from a group of 10 patients who had had lead intoxication and treatment, but in whom symptoms persisted for from six months to over one year after cessation of exposure (compensation involved).

GROUP 5: Patients attending the hematologic clinic who showed an unusual degree of punctate basophilia were studied for evidence of lead intoxication.

The series of normal persons (Group 1, above; see table 1) was studied originally to obtain data for normal standards of red blood cells, hemoglobin, white blood cells (filament-non-filament ratio) and reticulocytes. At the time this work was done it was the writer's belief that punctate basophilia was not present in the erythrocytes of normal individuals. It was only after our experience in encountering punctate basophiles in the smears of office patients that a second study of the blood films of the normal group

was made for stippled cells. Approximately one-half hour was devoted to study of each film. Jenner's stain was used, counter-stained with Giemsa's. Ordinary air fixation of films was employed. This has been our routine procedure in the hematologic clinic for the past 15 years. The group of office patients was selected at random, as the films showing punctate basophilia came to the attention of the technician. These blood films were counted later by each of us, and the average of two counts was used. Fifty fields of approximately 100 cells each were counted on each film. A Leitz special, direct light, and a 1-12 apochromatic lens were employed, without the use of a special eye-piece.

The amount of lead administered to the patients in Group 3 (see table 3) varied considerably, since we endeavored to avoid producing the more severe symptoms of lead intoxication. It should be stated that none of the group of patients with polycythemia knew that they were taking lead. As soon as any discomfort arose, the dosage of one capsule, 0.3 gm. given twice daily, was reduced. In spite of care in this respect, two patients suffered definite toxic episodes, and each was confined to bed for a period of about two weeks. The total amounts of lead taken were somewhat as follows: One patient under observation for two years took 60 gm. of lead acetate during that period; a second patient took 23 gm. over a period of six months, during which a severe toxic episode occurred; to one other patient, 20 gm. was the total amount administered over a period of two and one-half years. It is practically impossible to estimate the amount actually absorbed when lead is taken by mouth.

In the two patients who were given alkaline hematin solution (table 3), the punctate basophilia cell counts were within the range obtained for normal individuals. One received 1.5 gm. of purified hematin\* in normal saline solution, to which 0.2 per cent sodium carbonate was added, in order to dissolve the hematin. Amounts from 10 to 50 c.c. and concentrations from 0.1 to 0.6 per cent were used, both intramuscularly and intravenously. The administration of alkaline hematin solution was continued for two months. The second patient received 0.6 gm. of hematin diluted to 0.6 per cent, in normal saline solution to which 0.2 per cent sodium carbonate had been added. Injections of alkaline hematin in this patient were given for a period of one month.

The cases in Group 4 (see table 2) are self-explanatory. Group 5 (see table 4) is a small group of patients observed in the hematologic clinic, and one case seen in consultation. These patients represent unusual examples of punctate basophilia; all show either a hypochromic or hyperchromic, macrocytic anemia. One patient had pernicious anemia.

## RESULTS

*Table 1:* The mean of 92 punctate basophilia per million red cells is calculated for the entire group of 205 normal individuals, 50 of whom

\* Obtained from Eimer and Amend, New York.

showed no stippled cells. Seventy-five per cent of the group were positive. The highest count for individuals in the group was 400, per million red cells. The granules seen in the majority of the blood films were of the fine, well-diffused type. Many of the films had begun to fade by the time the writer re-studied them for punctate basophilia, some being three years old. In the series of office patients, the positives showed slight to moderate anemia, in 80 per cent of the cases. The standard by which anemia was judged was a hemoglobin below 90 per cent with a red cell count of 4.5 million or under.

TABLE I

Mean Number of Punctate Basophilic Cells per Million Red Cells in a Series of Apparently Normal Individuals, and in a Series of Office Patients Grouped According to Diagnoses

	Number of cases	Number of smears studied	Number of positive cases	Mean	Stand- ard devia- tion	Probable error of mean	Per cent positive
<i>Series:</i>							
A. Normal individuals . . . . .	205	205	155	92	93	$\pm 4.4$	75
B. Office patients . . . . .	400	400	234				58.5
<i>Positive Cases among Office Pa- tients (Series B), Grouped by Diagnoses:</i>							
1. Hypertension; cardiovascu- lar disease . . . . .		24	24	314			
2. Menopause; neurasthenia . .		39	39	215			
3. Anemia, chronic hypochro- mic; splenic anemia; lym- phoma . . . . .		60	53	500			
4. Chronic infection: focal, abdominal, pulmonary, pelvic . . . . .		38	38	290			
5. Cirrhosis of the liver . . . . .		18	5	780			
6. Malignant disease, with anemia . . . . .		8	8	210			
7. Arthritis, chronic . . . . .		18	18	267			
8. Bismuth absorption (syph- ilis) . . . . .		26	26	406			
9. Nephritis, chronic . . . . .		7	7	485			
10. Diabetes; colitis . . . . .		16	16	160			
Total . . . . .		254	234				
Average for all groups . . . . .				363			

A few patients with chronic hypochromic anemia had 5 million red cells per cu. mm. Two diagnostic groups of interest to the writer were those of chronic nephritis and cirrhosis of the liver, as the findings confirm previous observations made during the past 10 years.

*Table 2:* Blood smears of the group of eight men exposed to lead absorption but without symptoms, are examined once a month by the plant physician who makes basophile aggregation counts. Their mean count for punctate basophiles was 2,100 per million cells. All of the men in this group had been working at this same plant for over three years.

The next group of 10 men all had lead intoxication, but had been away from work and exposure for periods of from six months to over one year. They were all receiving compensation, because of persistence of symptoms, which is in marked contrast to the findings in our experimental group of patients (table 3), who invariably recovered from symptoms within a few weeks after administration of lead was stopped. The mean punctate cell count of 1,007 per million is somewhat higher than the finding of certain other investigators.<sup>5</sup> Mathew,<sup>28</sup> in an extensive survey of lead workers, found that in some cases there was no punctate basophilia a few days after exposure; in others, stippling persisted for several months after exposure ceased. He does not mention the counts for basophilia.

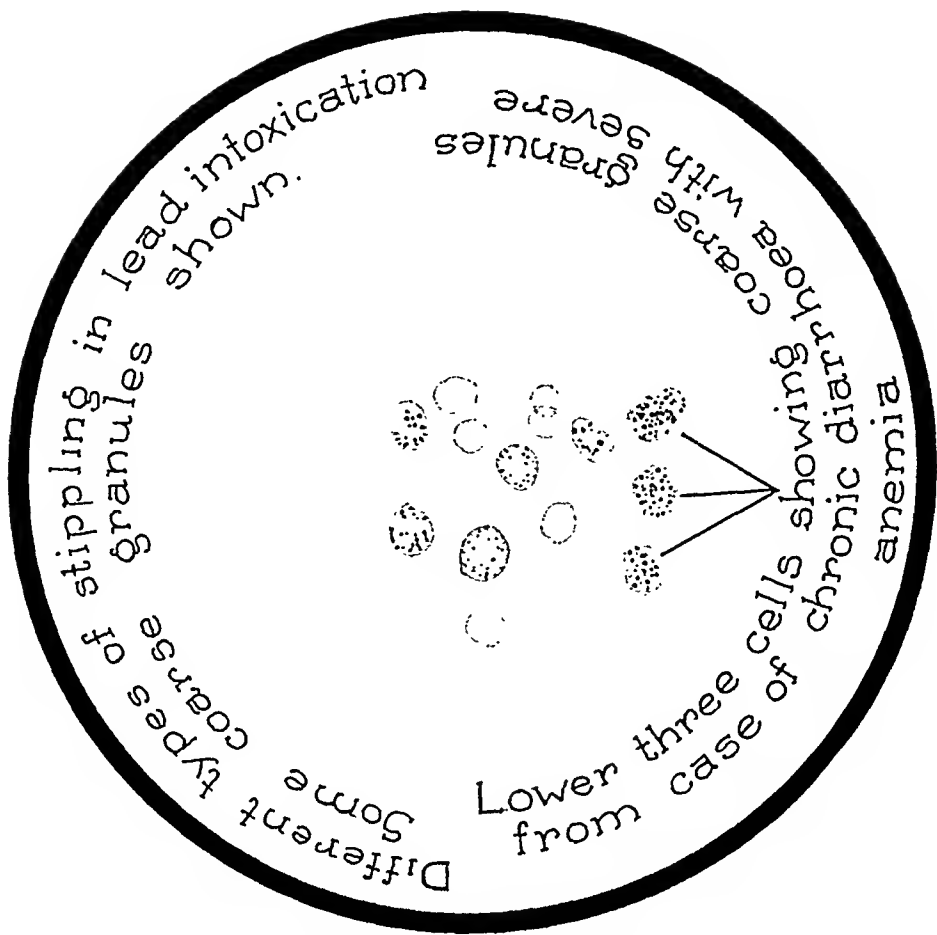
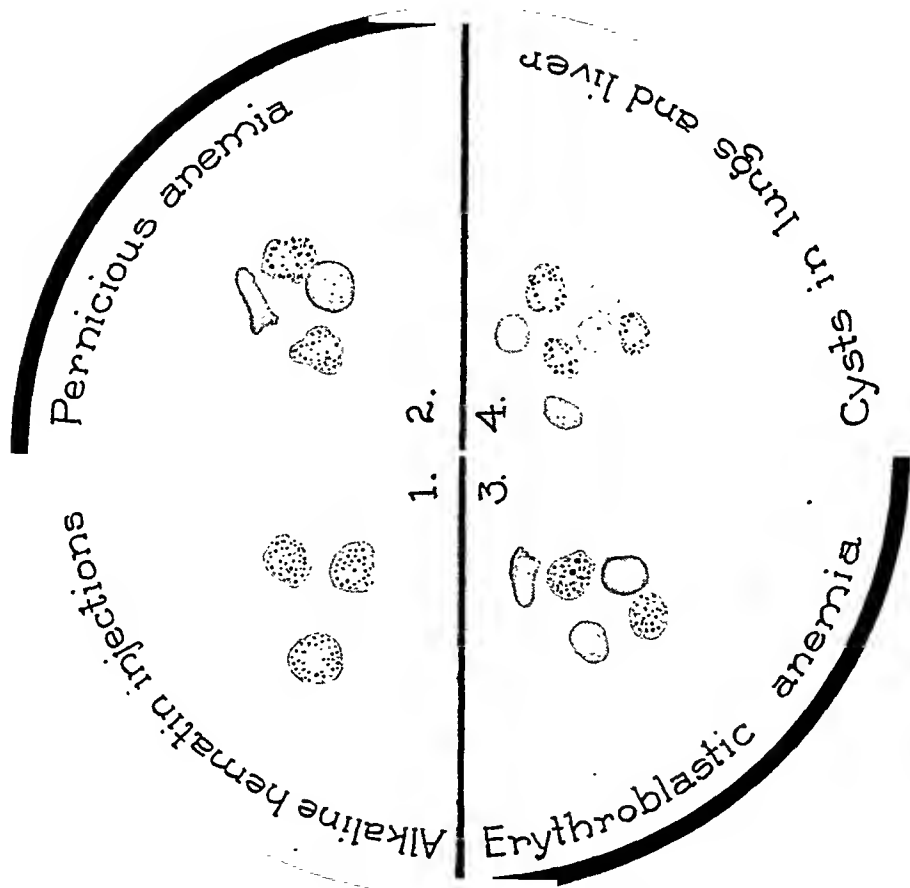
TABLE II

Two Groups of Lead Workers: One Free of Symptoms Following Exposure; the Other with Symptoms Persisting after Former Lead Intoxication but Having Had no Exposure for the Past 6 Months to 1 Year or More

Group	Number of cases	Smears examined	Exposure to lead	Mean punctate basophiles per million
Workers in paint manufacturing plant.....	8	8	Moderate	2,100
Bridge workers, workers in battery factory, and one automobile finisher.....	10	50	None for 6 months to 1+ years. Moderate to heavy original exposure	1,007

*Table 3:* This important table shows a mean punctate basophilia of 19,950 for the group of patients with polycythemia. The scatter is quite wide, the standard deviation being 15,400. This is due to the fact that punctate basophilia counts were made over a considerable period of time, including intervals when these patients were not receiving lead. The tolerance of individual members of the group varied markedly. One of the control individuals (with lymphatic leukemia) was very little affected symptomatically by the lead administered, nor were the red cells and hemoglobin decreased. The punctate basophiles in the blood of patients in this group rose promptly and to high levels. The granules produced by lead absorption in the films of this group tended to be large and quite distinct (see plate 1). This characteristic of punctate basophilia produced by lead has been emphasized by other workers.<sup>8, 9, 10</sup> The mean average of counts taken in the interval between the beginning of lead administration and the appearance of symptoms, was 2,250.

The two patients who received injections of alkaline hematin had mean punctate basophile counts of 5,250 and 2,092 per million red blood cells. These levels are much lower than the mean in our experimental lead group,



but one should consider the following facts: In the amounts administered, alkaline hematin is apparently non-toxic, as the injections produced no untoward symptoms and no after-effects that could be discovered. We had previously injected amounts up to 1.2 gm. per kg. of body weight in guinea pigs, with no discernible toxic effect. On two or three occasions where large amounts of fluid (4 c.c.) were injected subcutaneously, necrosis of the skin occurred. Per kg. of body weight, the guinea pigs received 1,000 times the dosage administered to our human subjects. Basophilic stippling in guinea pigs was much more marked than in either of the human subjects, reaching levels as high as 35,000 per million red cells.

Our attention was directed to the basophilic stippling effect on red cells, of alkaline hematin during some experimental work on thrombocytopenic

TABLE III

Incidence of Punctate Basophilia during Experimental Administration of Lead and of Alkaline Hematin Solution

	Number of cases	Number of smears examined	Mean punctate basophiles per million red cells	Standard deviation	Probable error of mean
<i>Administration of lead acetate in capsules, 0.3 gm. by mouth, to patients with:</i>					
1. Polycythemia vera . . . . .	5	150	19,950	15,400	$\pm 837$
2. Lymphatic leukemia . . . . .	2				
2. Same group as above, from start of lead until symptoms appeared..	7	37	2,250	1,030	$\pm 115$
<i>Administration of alkaline hematin solution (intravenous) to:</i>					
3. Patient with cardiac disease (stippled cells, 200 per million) . . . . .	1	21	5,250		
4. Elderly woman with cholelithiasis (stippled cells, 50 per million) . . . . .	1	37	2,092		

purpura in guinea pigs, conducted by M. R. Leonard and myself. Wade Brown<sup>29</sup> had reported that alkaline hematin possessed destructive effects on the thrombocytes of rabbits and guinea pigs. We were unable to reproduce this effect, but noted many punctate basophilic red cells following injections of alkaline hematin in guinea pigs. The writer used very conservative amounts of alkaline hematin in the experiment on the two patients above, in spite of the fact that this substance did not appear to be toxic to guinea pigs. Larger amounts would undoubtedly have produced higher stippled cell counts, and possibly a moderate degree of anemia as well. One fairly characteristic feature of the punctate basophilia produced by alkaline hematin, in both guinea pigs and humans, was the rapid disappearance from the blood stream after injections ceased.

*Table 4* records the punctate basophilic counts in patients with chronic diseases not complicated, or initiated, by lead absorption. Patient 3 was suspected of having lead intoxication. Some capsules she had been taking were found to contain a trace of lead, but the contents were later identified as being principally iron and ammonium citrate. Small doses of lead, even over a long period of time, would not produce such a marked degree of punctate basophilia without producing, in addition, definite symptoms and signs of lead intoxication. Also, qualitative tests for lead in this patient's blood and urine were negative. This patient is of further interest as one of the cysts of the lung showed a definite fluid level in the roentgenographic examination. This fluid may have been hemorrhagic and possibly contained products of red cell destruction, closely related to alkaline hematin solution.

TABLE IV  
Group of Miscellaneous Patients Showing a High Degree of Punctate Basophilia

Diagnosis	Number of patients	Number of smears examined	Duration of observation	Mean punctate basophiles per million red cells	Highest count punctate basophiles per million red cells
1. Nutritional anemia, hypochromic; lateral sclerosis; paraplegia	1	13	4 months	2,204	9,000
2. Chronic gastro-enteritis; extreme nutritional and metabolic disturbance; anemia, hyperchromic macrocytic . . . . .	1	25	6 months	12,000	52,000
3. Cysts of lungs, congenital; and bronchiectasis, chronic . . . . .	1	9	1 month	27,000	48,600
4. Myocarditis; achlorhydria; anemia, hypochromic . . . . .	1	4	3 weeks	14,000	22,000
5. Pernicious anemia; arteriosclerosis; chronic cholecystitis . . . . .	1	58	4 years	5,000	22,000

Its absorption into the general circulation may have caused the high degree of punctate basophilia. Patient 2 had a very severe anemia of the macrocytic, hyperchromic type, due to a marked nutritional disturbance, somewhat resembling sprue. There was a marked loss of calcium from certain of the long bones, giving a roentgenographic picture resembling that of multiple myeloma. The immature red cells were very numerous and showed basophilic phenomena, such as Cabot ring forms, Howell-Jolly bodies, Isaac's bodies, polychromasia, reticulocytosis and punctate basophilia. Patient 4 with pernicious anemia has been under observation for the past four years, during which time the levels of red blood cells and hemoglobin have never been normal, although in other respects he has made a satisfactory recovery under treatment with liver extract administered parenterally, and iron by mouth. He is an elderly individual with marked arteriosclerosis, chronic cholelithiasis, and chronic sinusitis with frequent acute "flare-ups" of

the sinus infection. His blood films always show punctate basophilia, at times rising to a high degree as is shown in table 4.

### DISCUSSION

What do our observations indicate as to the clinical significance of punctate basophilia in the erythrocytes of patients under investigation? It seems quite obvious that one should know the proportion of punctate basophilic cells per million red cells. In view of the more recent findings obtained by other investigators,<sup>8, 11</sup> and of our own data, the standard proposed by Schmidt,<sup>13, 5, 1</sup> and accepted by several German investigators,<sup>30, 3</sup> is much too low. They consider 100 punctate basophiles per million red cells as indicative of lead intoxication. Schnitter,<sup>31</sup> and other German investigators<sup>30, 3</sup> have stated that counts of 500 or more stippled cells per million red cells are pathognomonic for lead intoxication. This standard also must be far too low, if we are to accept present available data. According to our statistical treatment of the data in experimental lead intoxication (table 2), mean punctate basophilic levels between 16,000 and 23,500 per million red cells have a very high probability of being due to lead intoxication. As to basophilic stippled cell counts per se being specific for lead intoxication, we do not feel that scientific data support this assumption. At present there seems to be too much tendency among physicians to predicate a diagnosis of lead intoxication on the finding of a few punctate basophilic cells in the blood films, especially of men exposed to industrial hazards. The data obtained from the alkaline hematin experiments are evidence against the specificity of punctate basophilia as an index of lead absorption and intoxication. The effect of this agent on red blood cells suggests that hematin liberated in the body as the result of red cell destruction may be an important factor in the production of punctate basophilic granules.

### SUMMARY AND CONCLUSIONS

1. A group of 205 apparently normal individuals had a mean punctate basophilia of 92 cells per million red blood cells. Another group of 234 office patients, with widely varying clinical states, gave an average of 363 punctate basophiles per million erythrocytes.

2. A group consisting of five patients with polycythemia vera, and two controls with lymphatic leukemia, to whom lead was administered by mouth, had a mean of 19,950 basophilic stippled cells per million red blood cells. According to our data, statistically treated, this mean has a very much higher probability of being due to lead intoxication than to any other factor. Before symptoms of lead absorption appeared, this group had a mean basophilic stippled cell count of 2,250 per million red cells. In a group of eight workers exposed to lead but free of symptoms, the average count of punctate basophiles was 2,100 per million red cells. A group of 10 workers with former lead intoxication but who had been free from exposure for periods



of from six months to over one year, had an average of 1,007 basophilic stippled cells per million red cells.

3. After intravenous and intramuscular administration of alkaline hematin solution, two patients had average punctate basophile counts, respectively, of 5,250 and 2,092 per million red blood cells. Guinea pigs with larger doses of this substance had counts of punctate basophilia as high as 35,000 per million red cells. As hematin is a product of the breaking down of hemoglobin, these findings may lead to a better understanding of the manner in which punctate basophilia is produced in the erythrocyte. The production of stippled cells by administration of alkaline hematin solution is evidence against the specificity of these cells as an index of lead intoxication or absorption. Further evidence against this specificity is the high level of punctate basophilia found in the five patients listed in table 4, who had not been exposed to lead.

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## THE CHALLENGE OF APPENDICITIS \*

By REGINALD FITZ, M.D., F.A.C.P., *Boston, Massachusetts*

ALL men of Harvard and of Boston, particularly, are deeply interested in the history of appendicitis. For at the first meeting of the Association of American Physicians on June 18, 1886, R. H. Fitz, a Bostonian, the Shattuck Professor of Pathological Anatomy in Harvard University and Keeper of the Pathological Cabinet at the Massachusetts General Hospital, read a paper entitled, "Perforating Inflammation of the Vermiform Appendix with Special Reference to Its Early Diagnosis and Treatment." This paper was thoughtfully discussed by such distinguished internists as William Pepper of Philadelphia and E. G. Janeway of New York. This date may fairly be said to mark the birthday of the general clinical recognition of appendicitis in this country.

Described first at a meeting of physicians, the disease soon was claimed by the surgeons. In the past half century but six papers on the subject of appendicitis have been presented at meetings of the Association of American Physicians, whereas in the same period of time approximately ten times as many papers on this topic have been read at meetings of the American Surgical Society. These figures reflect very fairly the attitude of the entire medical profession toward appendicitis. Almost universally, appendicitis has come to be regarded as a surgical ailment, a disease taught by surgeons to medical students and practitioners. He is a bold medical man who raises his head in public and claims more than a bowing acquaintance with disorders of the *appendix vermicularis*.

It is not to be wondered at that the disease at first appeared of so great surgical interest for eventually the treatment is apt to be surgical rather than medical in nature. Naturally, therefore, surgeons have done most of the writing and talking about the diagnosis and treatment of appendicitis, its operative technic and postoperative complications, and, in fact, have done all in their power to make appendicitis as safe a disease as possible. They have accomplished a great deal. The record of the Massachusetts General Hospital serves well to illustrate what has taken place all over the country.

In the early days when to take out an appendix was something of an adventure, but few cases were operated on and their mortality was high. Little by little the surgeons grew familiar with the disease, operated earlier and with increasing temerity, and thus succeeded in reducing to a very low figure the operative mortality in any large group of cases.

During these years of improving surgical technic, however, a peculiar phenomenon has taken place. The total number of deaths from appendicitis has steadily increased. Each community with a collection of vital statistics duplicates the curious figures which have been observed in Massachusetts.

\* Delivered before the American College of Physicians, New York City, April 7, 1938.

PERFORATING INFLAMMATION OF THE VERMIFORM  
APPENDIX;

WITH SPECIAL REFERENCE TO ITS EARLY DIAGNOSIS AND TREATMENT.

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It appears that even the most recent systematic writers are by no means agreed as to the exact relation of inflammation of the cæcum and that of the appendix to peritonitis and perityphlitis. The vital importance of the timely and appropriate treatment of the disease in question is becoming more and more apparent. Such treatment is often postponed till hopeless, even if its application is at any time entertained. It was, therefore, to be anticipated that the critical consideration of a large number of unquestionable cases of perforation of the cæcal appendix might serve to make prominent the features essential for diagnosis and treatment.

In 1834, James Copland, in his *Dictionary of Practical Medicine*,<sup>1</sup> first discriminated between inflammations of the cæcum, the vermiform appendix, and the pericæcal tissue. Isolated cases of fatal inflammation of the appendix had been published from time to time before this date. Their importance did not become well recognized, however, till after Dupuytren's views had been made known concerning the relation of the cæcum to the production of what had hitherto been termed iliac abscess, or phlegmon of the iliac fossa. At the instigation of this eminent surgeon, Husson and Dance<sup>2</sup> published an article on the subject, apparently expressing his ideas. These were subsequently personally presented by him in his *Lectures on Clinical Surgery*.<sup>3</sup>

In consequence of the interest thus aroused, Goldbeck,<sup>4</sup> at the sug-

<sup>1</sup> Vol. i. p. 277.<sup>2</sup> Répertoire Gén. d'Anat., etc., 1827, iv. 164.<sup>3</sup> Leçons Orales de Clin. Chir., 1833, III. 330.<sup>4</sup> Ueber eigenth. entz. Geschw. i. d. rechten Hüftbeugegend, 1830.

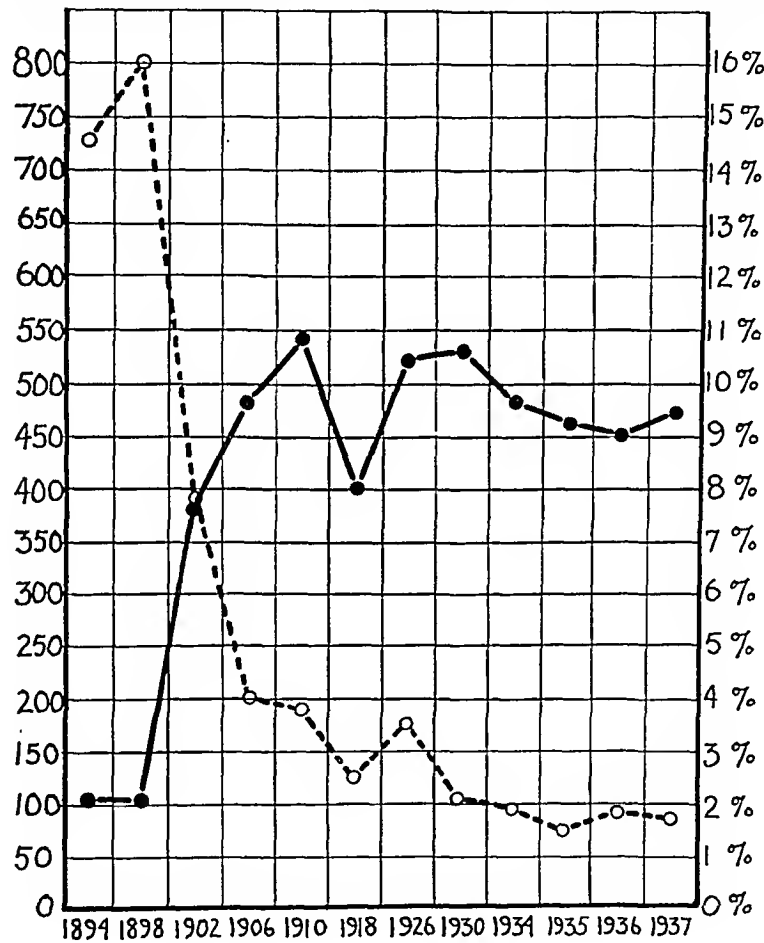
FIG. 1. Title page of the first American publication on appendicitis.

Here, for example, the death rate from appendicitis has increased from 8.7 per 100,000 in 1900 to 11.2 in 1936. In 1900 only 243 fatal cases of appendicitis were recorded; in 1936 there were 490.

It is well known that medical progress advances by cycles. The appendicitis cycle, seemingly, began at the first meeting of the American Association of Physicians in 1886, rotated at once from the hands of medical men to the surgeons who developed satisfactory operative treatment most skillfully; and now at the end of half a century it revolves again to the

internist in the paradoxical condition that has been mentioned—a common disease of low operative mortality in the hands of competent surgeons but in spite of this each year steadily proving fatal to a large number of people. During the next cycle can medical men add anything to the prophylaxis or

# APPENDICITIS IN MASSACHUSETTS GENERAL HOSPITAL



Number of Cases ●—●  
Percent of Mortalities ○---○

FIG. 2. The history of appendicitis in the Massachusetts General Hospital.

treatment of appendicitis by which the threat of this disease may be jugulated?

In his original description of appendicitis Fitz pointed out that the disease occurred most frequently among healthy, young people, especially males, though it might afflict persons of any age or either sex. The diag-

nosis in most cases was comparatively easy. Sudden, severe abdominal pain was the most constant first decided symptom, occasionally accompanied by a chill or nausea and vomiting. The temperature rarely was very high. If general peritonitis developed it began on the second, third, and fourth days after inflammation of the appendix was established. In fatal cases more than two-thirds died during the first eight days of the disease, and two-thirds of these died between the fourth and eighth days inclusive. If the question of operative treatment arose, such treatment should be applied early.

## APPENDICITIS IN MASSACHUSETTS

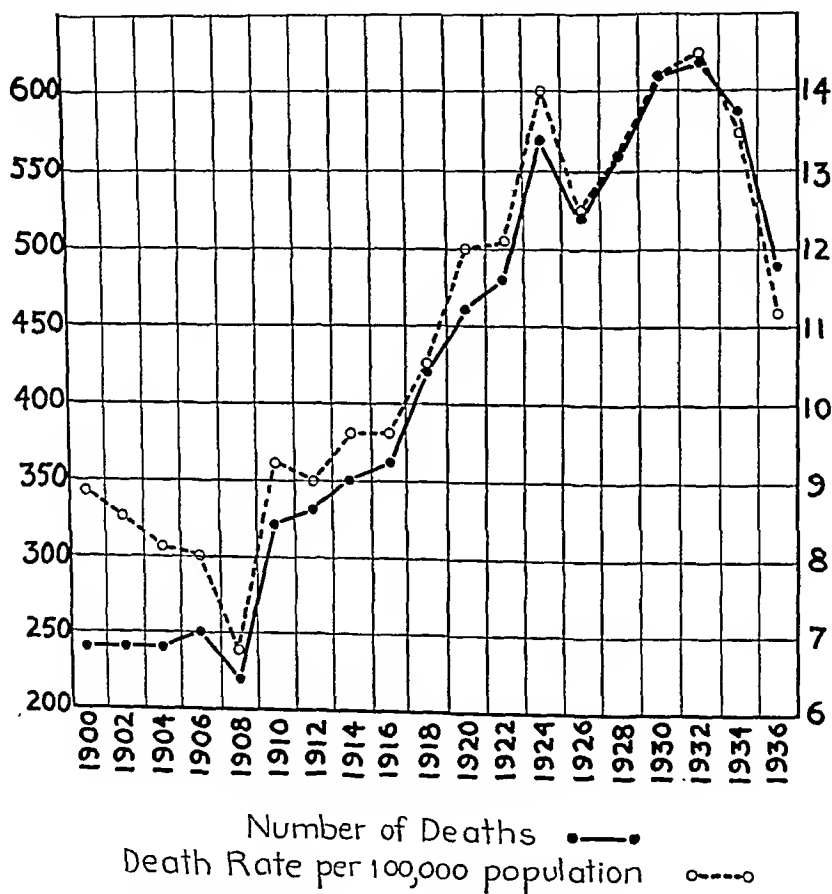


FIG. 3. Deaths from appendicitis in Massachusetts.

If delay in operation was warranted, this delay must be maintained until abscess formation took place and then the abscess should be incised as soon as it became evident.

The initial medical treatment essentially consisted in leaving the patient alone. To keep the bowels quiet was the first and last thought of the physician. A cathartic or laxative might be demanded by the patient or his friends and an enema be thought desirable. It appeared that the stirring up of peristalsis by any means was strongly contraindicated, for such a

procedure might be the means of at once exciting a general peritonitis. If operation was decided against and recovery ensued, the bowels opened spontaneously a few days after the discontinuance of the opium. Recovery from an attack of acute appendicitis often proceeded quickly, steadily, and without disturbance, the appetite and sense of well being returning long before the bowels were open.

Such, in brief, were the ideas concerning acute appendicitis in the days fifty years ago when the disease was in its infancy. They were based on sound clinical judgment and common sense, and still stand the test of time.

Appendicitis remains much as it was, a disease occurring most frequently among healthy, young adults, especially males, though it may afflict a person of either sex and any age. In a series of 2,600 cases recently treated in the Peter Bent Brigham Hospital, 68 per cent occurred in men and 32 per cent in women. The age distribution of these cases shows that nearly two-thirds were in people under 30 and that only 6 per cent occurred in individuals past 50.

The overwhelming majority of the Brigham Hospital case reports are to be found in the surgical records. Here appendicitis has been divided into five groups.

TABLE I  
A Clinical Classification of Appendicitis

Appendicitis	Cases	Deaths	Mortality
Unqualified .....	64	0	0
Chronic .....	808	1	.1%
Subacute .....	238	1	.4%
Acute .....	947	7	.7%
Acute with abscess .....	551	61	11%

This classification merely serves to illustrate what everyone knows; the chief mortality from appendicitis occurs in those cases which are perforated and have developed general peritonitis.

Dr. Nathaniel Faxon of the Massachusetts General Hospital has been kind enough to send me the number of deaths from appendicitis occurring in the wards of this hospital for the past three years; 1,373 cases were diagnosed as appendicitis and of these 23 died. Assuming that this mortality rate is not abnormal, one can estimate in round numbers from these figures and the reported deaths in the state, that in 1936 at least 25,000 cases of appendicitis were treated in Massachusetts. This gives some idea of the prevalence of the disease and its importance as a problem in public health.

The surgeons, and with much to be said on their side, blame two factors as chiefly responsible for the gravity of appendicitis. They claim that too often the disease is not recognized with sufficient promptness and that all too often cases before operation are mistreated with laxatives or cathartics. The experience of the Peter Bent Brigham Hospital bears out these claims. Of 65 fatal cases of appendicitis but 11 per cent were operated on within

24 hours of the onset of acute abdominal pain and but 37 per cent within the first 48 hours. No case was given the benefit of surgery within the first 12 hours. On the other hand, in 100 cases which recovered, 25 per cent were operated on within 24 hours of the onset of acute abdominal pain, and 50 per cent within the first 48 hours; 8 per cent received the benefit of surgery within the first 12 hours of the onset of symptoms. Evidently it is well still to be reminded that if the question of operative treatment arises, such treatment must be applied early to be effectual.

The cathartic situation is equally striking. In 65 fatal cases 74 per cent had taken some sort of cathartic before entering the hospital, while in 100 cases that recovered only 51 per cent had taken a laxative. Of the fatal cases, 31 per cent had utilized multiple laxatives like salts, enemas, and castor oil, combined and often repeated, whereas in the recovery group only 13 per cent had employed such drastic treatment. Surely in the early management of appendicitis to keep the bowels quiet should still be the first and last thought of the physician.

These remarks admittedly are trite and bring out nothing new or original. Every doctor recognizes that appendicitis is a common disease, that it must be treated early by surgery or else left to recover spontaneously, and that laxatives are likely to be injurious. But in spite of this general knowledge the deaths from the disease continue to climb. The question arises as to whether concerted action on the part of the medical profession to combat appendicitis is not indicated. Such an effort has been attempted in Philadelphia with some success under the stimulation of Dr. John O. Bower. Similar efforts might well be made in other parts of the country.

There are at least three logical lines of attack on a public health problem of this nature. The first is in our medical schools. Appendicitis should be taught as a medical disease. More stress should be laid by teachers of medicine on the fact that it is the family doctor who almost invariably is called in to make the diagnosis of appendicitis and to instigate treatment. Men going into practice must be taught more of the life history of appendicitis by the internist, of its diagnosis, of its initial medical treatment, of its dangers. In brief, more responsibility must be placed on the shoulders of medical teachers to instruct future general practitioners in regard to the early recognition and treatment of this disease.

Secondly, local medical societies must maintain a constant interest in appendicitis. Most doctors learn by repetition. The story of appendicitis must be repeated over and over. Apparently it can not be too strongly emphasized that appendicitis as a rule is an easy disease to recognize, that it begins with abdominal pain and usually with very slight fever, that almost any acute attack of painful indigestion is likely to be appendicitis, that stomachaches must always be taken seriously and not be treated over the telephone, and that the proper time to remove the acutely inflamed appendix is as early as possible after the diagnosis is established.



Thirdly, and perhaps nowadays this is the most important line of attack, a campaign of popular education must be instituted. The public at large appears eager to learn about medical matters and willingly will read or listen to sensible advice. In many people's minds there still is imbued implicit faith in the curative value of 'cleaning out the system' in the presence of any indigestion. A recent analysis of the common remedies sold without prescriptions in 14 representative Boston drug stores to customers who apparently wished to treat themselves illustrates the point very clearly. No doubt, too, in addition to tradition, the engaging advertisements that appear in magazines or on the air concerning laxatives and their uses are also a factor in their popularity.

TABLE II  
Popular Remedies Commonly Sold in Boston Drug Stores without Prescription

Remedies	Numbers of Stores
Saline Laxatives (Epsom Salts, Seidlitz Powders, Magnesium Citrate, etc.) . . . . .	14
Cough Medicine (Father John's, Rem, Syrup of Hydioidic Acid, Syrup of White Pine, etc.) . . . . .	13
Milk of Magnesia . . . . .	12
Cathartic Pills (Cascara, Alophen Tablets, Ex-Lax, etc.) . . . . .	12
Aspirin . . . . .	12
Sodium Bicarbonate . . . . .	10
Mouth Washes and Gargles (Listerine, Dobell's Solution, Alkalol, etc.) . . . . .	9
Things for Indigestion (Alka-Seltzer, Bisodol, Soda Mint Tablets, etc.) . . . . .	9
Mineral Oil . . . . .	9
Tincture of Iodine . . . . .	9
Disinfectants (ST 37, Sylpho Nathol, Lysol, Peroxide, etc.) . . . . .	9
External applications for coughs and colds (Musterole, Vicks Vapor Rub, etc.) . . . . .	9
Nose Drops (Argyrol, etc.) . . . . .	8
Castor Oil . . . . .	7
Boric Acid Powder . . . . .	7
Glycerin Suppositories . . . . .	6
Bromo Seltzer . . . . .	5
Boric Acid Ointment . . . . .	5
Zinc Oxide Ointment . . . . .	5
Mercurochrome . . . . .	5
Barbituric Acid Preparations (Luminal, etc.) . . . . .	5
Paregoric . . . . .	5

Medical authorities who arrange educational programs for laymen appear to be not enough concerned about the increasing importance of the appendix problem and must do something to combat the unwise use of laxatives. If men, women, and children can be taught to respect their intestines and to abandon the habit of using cathartics on the least provocation, many unnecessary deaths from appendicitis may be prevented.

Appendicitis, in spite of being a fashionable and well studied disease for more than 50 years, continues to slap our faces insultingly. It is easily recognized. Its treatment, on the whole, is satisfactory, yet it continues to kill each year an unnecessary number of people. May concerted action soon be taken by the American medical profession to meet the challenge of appendicitis and to relegate it to the rank where it belongs: a disease easily diagnosed, of no great danger, and when recognized early and submitted to proper treatment, readily amenable to cure.

# THE DEVELOPMENT AND IMPORTANCE OF HYPERTENSION IN CHRONIC BRIGHT'S DISEASE \*

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THE elevation of blood pressure characteristic of chronic Bright's disease is usually believed to occur in two ways: first, without any renal involvement whatsoever—primary or essential hypertension; second, as the result of renal insufficiency—secondary hypertension.

However, the development of increased arterial tension before impairment of renal function is present, occurs commonly in cases of chronic diffuse glomerular nephritis, whose initial, dominant, often sole sign is albuminuria. A study of 124 cases shows that 36 per cent had a normal blood

TABLE I

Analysis of 124 Cases of Albuminuria, Due to Chronic Bright's Disease, in Regard to the Development of Hypertension and Impairment of Renal Function. Attention Is Called to the High Percentage of Cases in Which Hypertension Develops Independently of Diminution of Kidney Function

Number of Cases	Per Cent	Elevation of Blood Pressure	Impairment of Renal Function
44	36	Normal	Normal
24 { 10	19 { 8	Moderate	Marked
14	11	Marked	Marked
56 { 20	45 { 16	Moderate	Moderate or none
36	29	Marked	Moderate or none

pressure, 19 per cent had an elevation of blood pressure associated with marked renal insufficiency, and 45 per cent had hypertension with little or no renal insufficiency. This analysis points to the order of events in chronic diffuse glomerular nephritis whose initial symptom is albuminuria, as being albuminuria first, hypertension next, and finally, renal insufficiency.

The cases of tables 2, 3 and 4 show how hypertension of marked degree may manifest itself in chronic Bright's disease characterized at the onset only by albuminuria, even in the absence of or coexistence of no more than a slight degree of impairment of renal function.

The hypertension occurring in patients with albuminuria often is the cause of death, as shown in tables 5 and 6.

The most common sequence of events when albuminuria exists, we have found to be: first, the evidence of hypertension followed by signs of renal insufficiency; if the patient survived the effects of the increased arterial

\* Read before the Meeting of the Association of American Physicians, Atlantic City, N. J., May 3, 1938.

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TABLE II  
Clinical Course of Albuminuria; Development of Hypertension

Date	Urine Analysis				Edema				B. P.		Renal Function			Blood		Remarks	
	Sp. Gr.	Alb.	RBC	Casts	Sub-cut.	Chol. Mg. %	Proteins Gm. %			Sys.	Dia.	Blood Mg. %			RBC mill.		Hb. %
							Tot.	Alb.	Glob.			Ur. N	NPN	Urea ratio			
1929 Jan.	31	+	0	Hyal. 0 Gran. 0 H													

J. L., male, aged 31 in 1929. Albuminuria discovered September 1928. Progression of Bright's disease by rising blood pressure which becomes the dominant feature. Note: the persistence of albuminuria, the blood pressure rises remarkably, while edema and anemia are absent, and only a minimal impairment of renal function is evident at any time.

TABLE III  
Clinical Course of Albuminuria: Development of Edema and Hypertension

Urine Analysis				Edema				B. P.		Renal Function				Blood		Remarks	
Date	Sp. Gr.	Alb.	RBC	Casts	Sub-cut.	Chol. Mg. %	Proteins Gm. %			Sys.	Dia.	Blood Mg. %			RBC mill.		Hb. %
							Tot.	Alb.	Glob.			Ur. N	NPN	Urea ratio			
1932 Oct.	24	++	++	Hyal. + Gran. ++	0				112	70						Albuminuria accidentally discovered 1931	
1933 Oct.	10	++	++	Hyal. + Gran. ++	0				140	80							
1935 Oct.	18	++	++	RBC +	0	223	5.5	3.8	1.7	150	80		35.0 30.0		4.5 90		
1936 Jan.		++	++	Hyal. + Gran. ++	±				130	70							
1937 Oct.	20	+++	++	Hyal. + Gran. ++	++	490	4.6	2.5	2.1	200	120	22.8	42.3	54.0	4.5 82	Changed to low prot. diet own accord (edema, anemia increased; blurred vision) High prot. diet; improved Vision clearer, very little edema; feels well	
1938 Jan.	16	+++	0	Hyal. + Gran. ++	++	704	4.3	2.5	1.8	204	130	25.4	42.8	59.2	3.0 76		
		+++	++	Hyal. + Gran. ++	++	600	4.2	2.2	2.0	186	102	26.6	43.5	61.2	4.0 76		
Feb.	18	+++	++	Hyal. + Gran. ++	±	393	4.4	2.6	1.8	172	108	27.9	42.0	66.3	3.8 82		
Mar.	20	+++	+	Hyal. + Gran. ++													

W. L., male, aged 24 (1937); albumin discovered 1931; gradual lowering blood albumin with rather sudden onset of edema; rapid development of hypertension; slight impairment of renal function; no anemia. Bad effect on edema, anemia, blood pressure and retinitis of low protein diet and remedial effect of high protein diet.

TABLE IV

Date	Urine Analysis				Edema		B. P.		Renal Function	Blood		Remarks
	Sp. Gr.	Alb.	RBC	Casts	Sub-cut.	Chol. Mg. %	Sys.	Dia.	Bld. Mg. % Urea N	RBC mill.	Hb. %	
1920 Mar.		++++		Gran. +++								Albuminuria began after mastoiditis and mastoidectomy
1922 Mar.	28	++++	+	Hyal. ++	0	240	112	84	9.3	5,272	70	
1923 Jan.	23	++++	+	Gran. +	0	480	114	82	15.0		80	
				Hyal. +								
Sept. 1924	20	++++	+	Gran. +	0	266	146	110	17.5			
				Hyal. ++								
Feb.	19	++++	++	Gran. ++	+		146	124				
				Hyal. ++								
Apr.	18	++++	0	Gran. ++	+		188	152	20.0	3,520		

Hospitalized. For subsequent clinical course see table 5

R. K., male, aged 8 in 1920. Albuminuria (evidently acute and chronic diffuse nephritis) since March 1920, following mastoiditis and mastoidectomy. Rise in blood pressure about three years later, which increased rapidly during the following year.

TABLE V

Date	B. P.		Blood Mg. % Urea N	Remarks
	Sys.	Dia.		
1924 4-19	228	178		Playing chess
20	232	194		
21	250	210		
22	244	184		Very drowsy
23	234	178		
24	210	160		
25	242	182		Convulsion
26	268	188	33.2	
27	182	122		
28	226	168	67.2	Semi-conscious
29	204	152		
30	220	162	53.6	
5- 1	206	162		Bright
2	202	164		
3	246	164	28.6	
4	228	156		Reading paper
5	246	172		
6	228	174	28.0	
7	202	162		Twitching
8				
9	200	140		
10	188	134	40.8	Bilateral kidney decapsulation
11	188	124		
12	228	158		
13	202	158	31.8	Brighter
14	218	164		
15	200	154		
16	192	160		
17	186	162		

Left hospital, died a few days later

R. K. (continued). Blood pressure during last month of life—the hypertension is the cause of death—renal decapsulation does not relieve blood pressure—the temporary rise in blood urea N following convulsion and after the operation may be due to protein destruction.

TABLE VI

Clinical Course of Albuminuria: Exacerbation of Hypertension: Hypertensive Death

Date	Urine Analysis				Edema		B. P.		Renal Function	Blood		Remarks
	Sp. Gr.	Alb.	RBC	Casts	Sub-cut.	Chol. Mg. %	Sys.	Dia.	Bld. Mg. % Ur. N	RBC mill.	Hb. %	
1929 May	07	+	0	0	0	232	198	136	38.2	4.2	69	Previously low protein diet. 3 transfusions (total 2500 c.c.). High protein diet. Drop in B.P. and blood urea
June	10	0	occ	0	0				43.0	4.4	80	
Sept.	10	0	0	0	0	189	172	114	24.9	4.8	72	
Oct.	11	+	0	0	0	188	166	112	22.6	5.1	86	
Dec. 1930	08	+	0	0	0	159	168	112	22.2	4.5	85	
Jan.	10	+	occ	0	0	158	162	112	17.8	4.9	85	
Apr.	09	+	0	0	0	160	156	114	25.4	5.2	85	
July	14	+	+	0	0	159	154	100	25.1	4.9	85	
Nov. 1931	10	+	+	0	0	165	158	104	24.4	5.0	80	
Feb. July	09	+	0	0	0		156	104	21.4	5.0	81	
							144	106	21.8	4.9	85	Sudden rise B.P.
Dec. 1932	06	+++	+	Hyal. + Gran. ++			196	130	25.8	4.6	86	
Jan. Apr.							212 204	136 140				

F.F., male, aged 43 in 1929. Albuminuria treated by low protein diet which apparently entailed anemia and diminution of renal function. A high protein diet and blood transfusions are followed by improvement in the anemia, renal function and blood pressure.

tension for a sufficient period the impairment of renal function would become more marked and retention uremia then was the cause of death. There were some cases of albuminuria that over a period of years (36 per cent, table 1) did not give evidence of either hypertension or impairment of kidney function.

The effect of a high protein diet in two cases is worthy of note though the number of observations is too few to make the conclusions anything more than suggestive. The patient of table 3 indulged in a low protein diet on his own initiative and shortly afterward suffered with anemia, edema and dimmed vision (albuminuric retinitis); a resumption of a high protein diet relieved all these complications and was followed by a lowering of the blood pressure. Similarly in another patient (table 6), when a high protein diet replaced a lacto-vegetarian diet, there was a lowering of the blood pressure, a reduction of the blood urea level and a complete disappearance of the albuminuric retinitis. Whether or not the improvement of the albuminuric retinitis in the one case, or its disappearance in the other, was fortuitous or could be attributed to the effect of the diet in a patient with anemia and no marked impairment of renal function, is an open question but the matter is worth further study.

The final rapid rise of blood pressure in the case given in table 6 might be ascribed to a high protein diet; on the other hand, a similar increase of

arterial tension shown in tables 4 and 5 resulted while a restricted protein regime was adhered to. Attention is called to these findings because we do not believe that a high protein diet is a cause of hypertension.

Two explanations suggest themselves for the comparatively early rise of blood pressure in chronic diffuse glomerular nephritis before distinct and persistent azotemia occurs: first, the hypertension may be brought about by a latent renal insufficiency which is not shown by the usual clinical tests since the latter only indicate a diminution of renal function when 50 per cent or more of the kidney tissue becomes inactive. Second, the progressive involvement of the kidneys incident to the nephritis may, through autolysis, produce a pressor substance akin to the "renin" which Tiegerstedt and Bergman<sup>1</sup> in 1898 extracted from rabbits' kidneys. This material might be regarded as similar to the "hypothetical effective substance" which Goldblatt<sup>2</sup> suggests may be produced through ischemia of the kidneys, though in chronic diffuse glomerular nephritis it would appear probable that the pressor material results from chronic inflammation and not ischemia. Autolysis of the kidney cortex, caused either by deprivation of blood supply to the kidney resulting from arteriosclerosis of the renal arteries, or effected through chronic nephritis, was proposed and enthusiastically championed as an explanation for arterial hypertension by H. Batty Shaw<sup>3</sup> in 1906.

#### SUMMARY

The relation of hypertension to chronic Bright's disease is a two-fold one. In the first place, hypertension may be primary, and the nephritis develop as the result of the hypertension; in the second place, the nephritis may be primary and the hypertension develop secondarily to it. In the latter group of cases it has usually been assumed that death occurred because of renal insufficiency and uremia. The follow-up on patients with chronic diffuse glomerular nephritis has shown that after a period in which albuminuria was the only abnormality, there often developed a gradually increasing arterial tension which, in many cases, proved to be the cause of death. The usual order of progress in chronic diffuse glomerular nephritis with an initial albuminuria, is, albuminuria first, hypertension next, and finally, renal insufficiency. It becomes evident on observation and treatment of cases of chronic diffuse glomerular nephritis that equal, if not more importance should be attributed to hypertension than to renal insufficiency as a possible fatal complication.

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# LIVER FUNCTION IN RHEUMATOID (CHRONIC INFECTIOUS) ARTHRITIS \*

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IN January 1937, we<sup>1</sup> published a preliminary report on the study of liver function in rheumatoid arthritis. The paper included results of the Azorubin S liver function test in 100 patients. It was shown that 73 per cent of the severe cases revealed liver dysfunction as determined by this method. Aware that no single test gives an indication of all the functions of the liver, the above findings prompted continuation of this study, using other liver function tests for comparison. The results obtained in 50 unselected cases will be reported in this paper.

Hippuric acid, bilirubin excretion (studies on 25 cases only), galactose tolerance, icterus index and albumin-globulin ratio determinations were selected for comparison with the Azorubin S test. Uniform conditions were maintained as far as possible. The following results were obtained.

## AZORUBIN S TEST

The technic used was described in the previous paper.<sup>1</sup> From 15 to 30 minutes was accepted as the normal appearance time of the dye. Shorter or longer periods indicated liver dysfunction in proportion to the deviation from the normal. In some patients the dye appeared within the normal time but the color was distinctly lighter than usual. This was attributed to inability of the liver to excrete the dye in concentrated form and was considered additional evidence of liver damage. Thus there were three possible types of liver dysfunction by this method: (1) delayed excretion; (2) too rapid excretion; and (3) reduced ability to concentrate the dye. The reduced appearance time is analogous to the observation of Whipple, Peightal and Clark<sup>2</sup> that, in patients poisoned with small doses of phosphorus, there is a hypersecretion of phenoltetrachlorophthalein attributed to the irritative effect of the phosphorus on the parenchyma of the liver. The inclusion of patients with reduced concentration ability makes the Azorubin S test even more sensitive as an indicator of liver dysfunction.

In the present series 60 per cent showed some evidence of liver dysfunction. The appearance time was reduced in fourteen. It was less than 10 minutes in five cases and between 10 and 15 minutes in eleven. The appearance time was delayed (30 to 60 minutes) in eleven cases. The power to concentrate the dye was reduced in five cases.

\* Read in abstract by Dr. Weiss before the Congress on Hepatic Insufficiency, Vichy, France, September 16, 1937.

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Klein and Levinson<sup>3</sup> pointed out that, in the bromsulphthalein test, some of the dye is phagocytosed by reticulo-endothelial cells, making the results inaccurate. This criticism may apply also to the Azorubin S test.

### HIPPURIC ACID EXCRETION

This test was described recently by Quick<sup>4</sup> and his procedure was followed throughout. The normal adult excretes about 3 gm. of benzoic acid in the form of hippuric acid in four hours. From 85 to 110 per cent of this amount is considered the normal range of excretion because of variations due to the size of the patient.

Abnormal findings were noted in 31 patients (62 per cent). The excretion was below 85 per cent in 20 (40 per cent). It was above 110 per cent in 11 (22 per cent).

Theoretically, a test based on the synthesis of hippuric acid should be a valuable measure of liver function because it determines ability to detoxicate which is one of the most important functions of the liver.

Quick<sup>4</sup> stated that the mechanism which conjugates benzoic acid with amino-acetic acid is probably the same as that which unites cholic acid with amino-acetic acid to form glycocholic acid, an important bile acid. The hippuric acid test also depends upon the capacity of the liver to synthesize amino-acetic acid. With the increasing realization of the importance of this substance in the physiology of muscle and perhaps other metabolic processes, any information concerning the capacity of the body to synthesize it should be useful clinically. Theoretically, the hippuric acid test, which depends upon these two important functions of the liver should furnish a more accurate estimate of liver insufficiency than tests depending upon the removal of dyes. The simplicity of the test makes it readily available to the clinician. It has the further advantage that sodium benzoate is inexpensive and of such low toxicity that it can be given in the presence of severe hepatic damage without unfavorable effects. The test can be repeated frequently which makes it valuable in following the course of liver disease and estimating prognosis.

Snell and Magath<sup>5</sup> stated that "in a large number of these tests performed at the clinic in the past two years, it has been noted that for patients who are not jaundiced the results closely paralleled the more familiar bromsulphalein test, while in cases of hepatogenous or obstructive jaundice the reduction in the synthesis of hippuric acid corresponded in a general way to the degree of hepatic injury noted at operation or necropsy."

### BILIRUBIN EXCRETION

The bilirubin excretion test was originally described by Eilbot<sup>6</sup> and was introduced in this country by Harrop and Barron.<sup>7</sup> The modified procedure of Soffer and Paulson<sup>8</sup> was used in these studies. Retention of more than 5 per cent of bilirubin after four hours was regarded as abnormal.

Positive results were obtained in 12 cases (48 per cent). This is slightly lower than the proportion of positive results with the hippuric acid and the Azorubin S tests. Since a positive reaction represents an extremely small increase above normal, it is doubtful whether such a slight increase can be determined with sufficient accuracy. Since excretion of bilirubin is one of the normal functions of the liver, test of this property should be of more fundamental significance than tests based upon excretion of foreign substances, such as dyes. Soffer and Paulson<sup>8</sup> reported the results of 18 cases in which there was slight, but clinically well-defined, liver damage. The bilirubin excretion test indicated dysfunction in 16 and the bromsulphthalein test in only three cases. In 15 cases in which there was no clinical evidence of liver damage, but in which hepatic involvement was suspected, 12 were positive with the bilirubin excretion test but only three were positive with the bromsulphthalein test. When the bromsulphthalein test was positive the bilirubin excretion test was always positive also. They attributed the increased sensitivity of the bilirubin test to the following factors: (1) the excretory function of the liver is measured by a substance excreted normally; (2) the excretory function of the liver is probably the first to be disturbed; (3) other excretion tests are based on the power of the liver to selectively remove foreign substances, such as dyes, from the blood stream.

Injected bilirubin is excreted in toto by the liver, except in obstructive jaundice, whereas dyes such as bromsulphthalein may be partially phagocytosed by the reticulo-endothelial cells.

#### GALACTOSE TOLERANCE TEST

There is a voluminous literature on the value of this test but only seven (14 per cent) of the patients in our series showed positive results (excretion of 2 grams or more). The test does not appear to be sensitive enough to detect chronic or mild liver damage.

Tunen and Bockus<sup>9</sup> compared galactose tolerance with hypoalbuminemia and suggested that the former was more significant in acute than chronic liver damage, while the reverse was true of the latter. Since our series comprised patients with possible chronic liver damage this may account for the small number of positive results.

Soskin and Mirsky<sup>10</sup> demonstrated that there were apparently three stages of liver damage and that the results obtained with the dextrose tolerance test depend to a considerable extent upon two factors: the stage of liver damage; and the amount of dextrose used. They pointed out that extrahepatic tissues can dispose of approximately 0.25 gram of dextrose per kilogram per hour and that the administration of less than this amount yields curves simulating better than normal hepatic function, while the administration of larger amounts of dextrose leads to an accumulation in the blood, simulating a "diabetic" curve. They concluded that, under favor-

able circumstances, a supposedly normal dextrose tolerance curve may represent a greater degree of liver damage than a "diabetic" curve and less damage than a supernormal curve. The unsatisfactory results with galactose tolerance in our cases may be due to similar influences. Banks and his co-workers<sup>11</sup> showed that the test was positive in 25 to 40 per cent of cases in which obstructive jaundice had persisted for a sufficiently long time to injure the hepatic parenchyma and was consistently negative in portal and biliary cirrhosis. Snell and Magath<sup>5</sup> stated that "so far as we have been able to determine, the test has no value whatever in cases in which the patients are not visibly jaundiced."

#### ICTERUS INDEX

If less than 8 is accepted as the normal icterus index, 22 (44 per cent) of the findings were abnormal. Although this proportion approximates those obtained with bilirubin and hippuric acid tests, there is rather wide variation from normal in patients with no apparent evidence of liver damage. This cannot be attributed to experimental error because one of us (W. B. R.) has shown<sup>12</sup> that there is only a slight daily variation in the same patient and that the experimental error does not exceed 0.7. Therefore, the test should receive further study before it is accepted as a measure of liver dysfunction.

#### THE ALBUMIN-GLOBULIN RATIO

Less than 4.5 mg. of albumin per 100 c.c. of blood serum was considered abnormal. There was hypoalbuminemia in 34 cases (68 per cent).

There was an abnormal A-G ratio (less than 2) in 38 cases (76 per cent). There was a reversal of the A-G ratio in some patients having normal liver function by other tests, and 8 patients with a normal A-G ratio showed positive results with the other tests.

Snell<sup>13</sup> pointed out that "one of the fairly constant effects of parenchymatous hepatic disease is reduction of the albumin-globulin ratio; that these changes are most probably related to deficient production of protein by the liver, and that for this reason they may have some diagnostic and prognostic significance; and finally, that the serum albumin is often at or near a level which makes the production of ascites and edema relatively easy."

Tumen and Bockus<sup>9</sup> suggested recently that the diagnostic value of reversal of the A-G ratio has been overemphasized. They concluded that hypoalbuminemia was the most constant change noted, that it was present at one time or another in every case of chronic, advanced liver disease and in most cases of obstructive jaundice, and that the reversal of the A-G ratio was not as significant or constant as the loss of serum albumin. Davis,<sup>14</sup> however, did not find hypoalbuminemia more frequently than a change in the A-G ratio in patients with rheumatoid arthritis.

In the present series, reversal of the A-G ratio was even more constant than hypoalbuminemia and these findings were substantiated in a much larger, independent series of cases. Although hypoalbuminemia may indicate liver dysfunction, our findings do not indicate its superiority over the A-G ratio.

## COMPARISON OF THE TESTS

Because the A-G ratio, galactose tolerance and icterus index were not considered reliable they will be eliminated from further discussion. The

TABLE I  
Comparison of Liver Function Tests in Patients with Rheumatoid Arthritis

	Azorubin S (Mins.)		Hippuric Acid (%)		Bilirubin Excretion (% retent.)		Galactose Tolerance (grams)		Icterus Index		A-G Ratio	
Normals	15-30		85-110		<5		<2		<8		>1.99	
	Nor.	Abnor.	Nor.	Abnor.	Nor.	Abnor.	Nor.	Abnor.	Nor.	Abnor.	Nor.	Abnor.
Normal Azorubin S												
M. S.	20		104		0		1.4		4.0		2.0	
F. F.	25			73			1.4			9.0	2.0	
A. P.	25		88		0		0.5			8.0		1.5
A. S.	20			128			1.7		6.6			1.2
M. G.	21		104		0		1.0		7.2			0.8
C. F.	29		96				1.5		7.0			1.2
C. R.	30		106		0.4		0.9		7.5			1.3
J. B.	18		101				0.5		6.2			1.4
M. H.	20		86				0.9		7.4			1.3
F. P.	15		110		1.6		0.4			8.4		1.2
F. W.	24			136		7.0	1.0		7.0			1.1
M. S.	21		104		0.6		1.4		4.0			1.2
L. O.	19			127		8.0	0.9		7.8			1.6
F. F.	24			80	0.7		1.4			9.0	2.0	
N. D.	20		87		0.4		1.0		7.5			1.2
T. A.	17		87		0.9		0.5			8.4		1.1
M. C.	26		105				0.8		7.5			0.9
M. M.	21			73			0.4			8.5	2.4	
J. T.	28		110				0.3		5.7			1.6
V. L.	19		96					2.2		11.5		1.1
Reduced Azorubin S												
O. K.		12		64					7.0			1.4
F. B.		9	93									1.0
S. C.		13		116			1.2			9.6		1.3
J. B.		8		65	0		1.7			8.0		
C. G.		11		67		12.6		2.5		9.7	2.8	
S. M.		12		146	0		1.1			8.0		1.2
W. B.		8		131		9.4	0.6			8.2	2.4	
M. deM.		10		70		21.0	0.4			10.4	2.2	
E. D.		7		127	4.0			3.7	6.6			1.0
C. O'B.		12		75		7.0	1.5			8.0		1.8
F. B.		13		114				3.2		8.5		0.9
L. B.		14		71			0.1		7.6		2.0	
S. E.		8		120			1.3		7.0			1.5
C. S.		13	106				0.8		5.6			1.3
							0.4		7.0		2.3	

TABLE I—*Continued*

	Azorubin S (Mins.)		Hippuric Acid (%)		Bilirubin Excretion (% retent.)		Galactose Tolerance (grams)		Icterus Index		A-G Ratio	
Normals	15-30		85-110		<5		<2		<8		>1.99	
	Nor.	Abnor.	Nor.	Abnor.	Nor.	Abnor.	Nor.	Abnor.	Nor.	Abnor.	Nor.	Abnor.
Delayed Azorubin S												
H. C.		40	107		1.0			3.3	5.0			1.0
C. C.		35		80			1.0			8.7		0.6
M. M.		35	88			14.5	0.4			8.4	2.4	
M. D. M.		40		69		21.0		3.8	6.6			1.1
C. G.		33		67		13.0	1.1			8.0		1.2
S. C.		45		59			0.6			8.9		1.2
J. G.		37		62		28.0	1.0		6.6			1.3
T. W.		41		135			0.7		5.8			1.1
J. W.		40		70		16.0	0.4		7.2			1.3
M. R.		40		53	0		0.8		6.6		2.4	
M. N.		60		73	0.6			2.6	4.0			1.4
Reduced Concentration of Azorubin S												
A. G.				114			0.6		6.8			1.6
H. S.				78		6.4	0.4			8.3		1.3
M. M.			92				0.4		7.5		2.1	
E. W.				68			0.2			9.1		1.5
L. C.				70			0.4			9.1		1.7

Azorubin S test was positive in 60 per cent, hippuric acid in 62 per cent, bilirubin excretion in 48 per cent. The three tests combined gave evidence of liver damage in 36 (72 per cent) of the cases. Therefore, the Azorubin S, hippuric acid and bilirubin excretion tests were considered the most reliable of the tests studied. The Azorubin S test agreed more closely with clinical evidence of liver damage than any other single test.

Table 1 indicates that no single test should be used as the sole basis for diagnosis of liver dysfunction. It is necessary to correlate the clinical history with the physical findings and the results of various tests.

Only five of those patients with abnormal Azorubin S test failed to show abnormal findings with one or more of the other tests. In those with reduced appearance time, two were negative with other tests. Lyon and Wirts,<sup>15</sup> in discussing our previous paper, questioned whether the reduced appearance time in the Azorubin S test denoted liver damage. In the present study it was found that, when there was a reduced appearance time and reduced concentration ability, there were other indications of liver dysfunction. In patients with delayed appearance time, all showed abnormal findings with one or more of the other tests. In patients with reduced concentration ability, only one did not show abnormal findings with other tests. Because of this agreement between the Azorubin S test and other

evidence of liver dysfunction and the high percentage of positive results obtained by it, we believe the Azorubin S test is the most valuable of those studied. It has, however, the disadvantage of requiring passage of a duodenal tube and is time-consuming.

In addition to the tests described in this paper, the serum bilirubin, Van den Bergh reaction, cholesterol and cholesterol esters, urobilin and urobilinogen, and phosphatase activity studies were made in a number of cases but, in general, no added information was obtained. This agrees, in general, with the findings of Snell and Magath.<sup>5</sup>

### SUMMARY AND CONCLUSIONS

1. A high proportion of patients with rheumatoid arthritis showed evidence of liver damage as determined by the Azorubin S, hippuric acid and bilirubin excretion tests. The icterus index, galactose tolerance and A-G ratio were considered unsatisfactory.

2. The hippuric acid test and the A-G ratio gave the highest proportion of abnormal findings.

3. When the Azorubin S test showed abnormal findings, one or more other tests also were abnormal.

4. Because of this agreement and because it agreed more closely with clinical evidence, it was considered most suitable for detecting chronic liver damage.

5. Technical errors and lack of specificity in the different tests make it desirable that more than one test be used.

We wish to express our thanks to Miss Santa Teti who carried out the technical studies of this series, and to Mr. George H. Chapman for many valuable suggestions.

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# SERUM PROTEINS IN RHEUMATOID DISEASE\*

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## INTRODUCTION

CHRONIC arthritics present a variety of symptoms which involve deviations from normal protein metabolism.<sup>1</sup> This is graphically evident in gout, one of the smaller groups of rheumatoid disease, which is characterized by the accumulation of urates in articular and other tissues. This local feature is associated with systemic evidence of an abnormal metabolism of nucleoprotein. The absence of this conspicuous feature in the other and larger groups of rheumatoid disease has diverted attention from a consideration of such deviations in protein metabolism as are presented by them. These deviations include both local and systemic features. One large group, namely atrophic arthritis, involves a proliferation of the synovial membrane.<sup>2</sup> This pathological process necessitates an increased production or new formation of protein. Another large group of cases, constituted by hypertrophic arthritis, is marked by degenerative changes in the articular cartilage.<sup>2</sup> This change involves a deviation from the normal physical state of the conjugated protein of which cartilage is partly composed. An extra-articular tissue which is sometimes modified in arthritis is the nail, as shown by the fact that keratin, the protein component, is often relatively deficient in one of its parts, namely, cystine.<sup>3</sup> This is not known to be characteristic of any one type of chronic arthritis<sup>4</sup> and is also to be observed in other chronic diseases.<sup>5</sup>

General metabolic and physiological disturbances, in addition to those occurring within the joints, develop in arthritis coincidentally with the joint manifestations. Some of these extra-articular phenomena also involve disturbances from the normal course of protein metabolism. For example, many cases present a secondary anemia which reflects some disturbance in the course of normal hemoglobin and red cell production. Some cases present a peripheral edema which does not seem to be wholly due to circulatory factors in the ordinary sense of the word.<sup>6</sup> It is conceivable that such an "edema" may be due to a reduced colloid osmotic pressure of the blood, a factor which is chiefly determined by the level of the albumin of the plasma. This is not always the case, however, and another factor to be considered is an increased capillary permeability. The sera of many cases of atrophic arthritis show high agglutinin and precipitin titers with streptococci and chemical fractions obtained from them.<sup>7</sup> These antibodies appear

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because of the presence of proteins having properties different from the serum proteins normally present.<sup>8</sup> The blood of many atrophic arthritics exhibits a rapid sedimentation of the red cells.<sup>9</sup> This accelerated sedimentation rate reflects a modification in the colloidal medium in which the cells are suspended and this is chiefly determined by the proteins of the plasma.<sup>10</sup> Davis,<sup>11</sup> and Alred-Brown and Munro<sup>12</sup> have reported data showing that the sera of atrophic arthritics have decreased albumin-globulin ratios and that the sera of hypertrophics show some but less deviation from normal.

If, as the foregoing considerations indicate, the disturbances in the metabolism of protein are significant, it becomes desirable to evaluate further the extent to which deviations are apparent in various types of rheumatoid disease in various stages of illness, and to evaluate the probable influences of such deviations. These considerations suggest the possibility that further detailed study of protein metabolism in arthritis may yield additional information regarding the nature of the disease. The simplest approach to these problems may be obtained by a statistical analysis of the levels of various protein fractions in the blood sera of groups of rheumatoid patients. To this end a statistical analysis is presented of the findings obtained in the analysis of proteins in a series of 177 patients with various types of rheumatoid disease, 10 patients presenting a variety of other serious clinical conditions and 15 normals.

#### MATERIALS AND METHODS

The group of patients under observation includes both ambulatory and hospitalized subjects suffering from various kinds of rheumatoid disease and exhibiting different degrees or stages of clinical activity. The classification of cases is made on the basis of a comprehensive clinical study.

Specimens of venous blood were allowed to clot, the sera separated and the total protein, the albumin and globulin, estimated according to the general method of Howe, using a micro-Kjeldahl technic.<sup>13</sup> The data have been summarized in tables showing the number of cases presenting values in given ranges.

The data on the levels of total serum proteins are presented in table 1. Total protein values ranging from 6.0 to 9.2 grams per 100 ml. have been arbitrarily arranged in intervals differing by 0.4 gram per 100 ml. The number of instances is tabulated in which various levels were encountered according to clinical groupings. Such a tabulation shows the frequency with which various values were found as well as the respective relations of these values to the several groups of arthritics studied. Reference to table 1 shows that a few patients in each group present total protein levels which are below those encountered in the normal subjects. However, no values were found which were equal to or lower than the critical level for edema formation. None of the patients showed edema of the degree presented by nephrosis. It is further evident that no consistent deviation char-

TABLE I

Statistical Analysis of the Levels of Total Protein in the Sera of 177 Cases of Rheumatoid Diseases, 10 Cases of Non-Rheumatoid Disease and 15 Normals

Diseases, 10 Cases of Each																	
Type of Cases	Number of Cases																
	Total	Range of Total Protein Grams per 100 ml.															
		6.0-6.4		6.4-6.8		6.8-7.2		7.2-7.6		7.6-8.0		8.0-8.4		8.4-8.8		8.8-9.2	
		F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
Atrophic																	
Severe.....	48			3		3	4	7	6	3	5	4	2	1	3	2	5
(Spondylitis).....	(14)								2		5		1				6
Atrophic Moderate.....	27	1			1	3	1	5	2	7		4	1	2			
Hypertrophic.....	52	3		2	1	5	5	12	4	6		7		4		2	1
Mixed A and H.....	34		1	1	1	3	1	2	2	9	4	2	2	2		2	2
Syphilitic.....	5					1		1		2			1				
Tuberculous.....	2				1												1
Gout.....	4						2		1		1						
Miscellaneous Rheumatoid.....	5					1				1	2					1	
* Non-Rheumatoid.....	10		1	1	1	2	1		1	1		1		1			
Normal.....	15									9	2	1	1		1	1	

\* Severely ill patients.

F—Female Subject.

M—Male Subject.

acterizes any one group, with the exception that the spondylitic cases show a trend toward a level of total protein higher than normal.

An analysis of the data on the levels of albumin in the sera is shown in table 2. The data are arranged after the same general plan described above

TABLE II

Statistical Analysis of the Levels of Albumin in the Sera of 177 Cases of Rheumatoid Diseases, 10 Cases of Non-Rheumatoid Disease and 15 Normals

Type of Cases	Number of cases																				
	Total	Range of albumin levels																			
		grams per 100 ml.																			
		2.2 2.6		2.6 3.0		3.0 3.4		3.4 3.8		3.8 4.2		4.2 4.6		4.6 5.0		5.0 5.4		5.4 5.8		5.8 6.2	
		F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M		
Atrophic																					
Severe	48				2	3	4	2	1	5	5	8	4	6		6		1	1		
(Spondylitis)	14				1					4		3		5				1	1		
Atrophic Moderate	27																				
Hypertrophic	52				2	1			1	2	2	8	4	6	3	7		4	1		
Mixed A and H	34	1				1			1	3	3	2	4	9	4	16	2	1	1	1	
Syphilitic	5					1	1	1		5	3	2		6	1	5	2	1	3	1	1
Tuberculous	2									2		1				1	1				
Gout	4												1			1	1				
Miscellaneous Rheumatoid	5									1					2		1				
* Non-Rheumatoid	10										1			1		1		1			1
Normal	15				1	1	1	1		4	1		1		3		4	2	4	1	1

\* Severely ill.

for total proteins. Albumin values from 2.2 to 6.2 grams per 100 ml. are listed in 0.4 gram per 100 ml. intervals. The number of cases presenting values within each level is tabulated. It is evident that no clinical group of arthritics is characterized by a striking deviation from the normal distribution. It may be worthy of note, however, that a considerable number of all groups show instances in which lower values are encountered than among the normals.

A statistical analysis of the data showing the frequency of various levels of globulin in the sera is presented in table 3. Globulin levels ranging

TABLE III  
Statistical Analysis of Data Showing the Incidence of Various Levels of Globulin in the Sera of Rheumatoid and Non-Rheumatoid Subjects

Type of Cases	Number of subjects																				
	Total	Range of globulin levels																			
		grams per 100 ml.																			
		1.2 1.6		1.6 2.0		2.0 2.4		2.4 2.8		2.8 3.2		3.2 3.6		3.6 4.0		4.0 4.4		4.4 4.8		4.8 5.2	
		F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
Atrophic																					
Severe.....	48			1		4	1	1		5	6	6	4	4	6	1	4	3	1	1	
(Spondylitis).....	14									2	2		4		3						
Atrophic Moderate.....	27	1		1		3	2	7	2	6	1	3		1							
Hypertrophic.....	52	1		2	1	7		8	6	14	2	4	1	3	1	1		1			
Mixed A and H.....	34			2	2	1	2	4	2	7		2	4	4	2	1					
Syphilitic.....	5					1				2			1		1						
Tuberculous.....	2							1							1						
Gout.....	4					1			2		1										
Miscellaneous																					
Rheumatoid.....	5							1	2	1						1					
* Non-Rheumatoid.....	10			1				1		1	1	1		1	1	1		1	1		
Normal.....	15					1	1	5	3	4				1							

\* Severely ill.

from 1.2 to 5.2 grams per 100 ml. are tabulated in 0.4 gram per 100 ml. intervals. The number of instances in which each level was encountered is tabulated. A few apparently significant deviations from the normal range appear. The group of severe atrophic arthritics shows a large portion of cases presenting globulin levels higher than those encountered among normals. The group of atrophic spondylitics all show levels of globulin higher than normal. These figures appear more significant when compared with the group of moderate atrophic arthritics in which normal levels are apparent. The group of hypertrophic arthritics also presents a contrast to the normals though not so marked as that just mentioned.

The ratios of albumin to the globulin in the sera are shown in table 4. The data are presented in the manner outlined above. The range of albumin globulin ratios or quotients from 0.4 to 3.4 is divided into arbitrary intervals differing by 0.3. The number of cases presenting values at each

level is tabulated. Sixty per cent of severe atrophics show values lower than any normal. Seventy-eight per cent of the atrophic spondylitics show ratios lower than any normal. This is in marked contrast to the number of atrophic patients with moderate involvement in which only 4 per cent show significantly low values. While only 7 per cent of the hypertrophics show ratios lower than any normal, 42 per cent of them show ratios at the lower limits of normal. The remaining rheumatoid groups showed little constancy of deviation from the normal range. The severely ill non-rheumatoid subjects all presented significantly low albumin-globulin ratios. This fact is important in showing that a low albumin-globulin ratio is not to be regarded as pathognomonic for the atrophic arthritic. The significant fact

TABLE IV

Statistical Analysis of Data Showing the Incidence of Various Albumin-Globulin Ratios in the Sera of Rheumatoid and Non-Rheumatoid Subjects

Type of Case	Total	Number of cases															
		Range of albumin-globulin ratios															
		0.4 0.7	0.7 1.0	1.0 1.3	1.3 1.6	1.6 1.9	1.9 2.2	2.2 2.5	2.5 2.8	2.8 3.1	3.1 3.4						
		F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
Atrophic																	
Severe.....	48			5	5	7	12	3	5	3	1	3	1	1	1		
(Spondylitis).....	14			3	3		8		1	1							
Atrophic Moderate.....	27				1	1	2	5	1	5	2	6	1	2	1	1	
Hypertrophic.....	52		1		1	2	14	4	13	1	6	2	3	1	1	1	
Mixed A and H.....	34	1		2	2	4	7	1	5	5	2		1	1		2	1
Syphilitic.....	5				1		2	1					1				
Tuberculous.....	2						1						1				
Gout.....	4					1				1			1				
Miscellaneous																	
Rheumatoid.....	5				1				2		1				1		
* Non-Rheumatoid.....	10		1	2	1	3	1	1									
Normal.....	15						1		4		4	3	2		1		

\* Severely ill.

is that the severe atrophic, like some patients seriously ill with other diseases, shows evidences of a systemic disturbance in protein metabolism.

A summary of the average levels of the protein fraction in the sera of the cases included in this series is shown in table 5. It is evident that the very seriously ill non-rheumatoid group presents the lowest average ratio, namely, 1.05. The atrophic spondylitics present an average ratio of 1.13 and the group of severe atrophics 1.27. The moderate atrophics show an average level of 1.83 which is close to that in the normals, namely, 1.99. The hypertrophic arthritics show an average value of 1.70 which is intermediate between the normal and the severe atrophic group and lower than the moderate atrophic group. The group of mixed cases is intermediate between the hypertrophic and the severe atrophics, a fact which is in harmony with the general clinical picture, which is likewise intermediate between the two. The cases of gout and the miscellaneous rheumatoid dis-

cases approximate the moderate group with respect to albumin-globulin ratio. The syphilitic and tuberculous groups more nearly approximate the cases of mixed rheumatoid disease.

TABLE V

Summary of the Average Levels of Protein Fractions in the Sera of 177 Cases of Rheumatoid Diseases, 10 Non-Rheumatoid Disease and 15 Normals

Type of Case	Number of Cases	No. of Determinations	Average							
			Total Protein		Albumin		Globulin		Alb.-Glob. Ratio	
			Gm. per 100 ml.	Per cent of Normal	Gm. per 100 ml.	Per cent of Normal	Gm. per 100 ml.	Per cent of Normal	Quotient	Per cent of Normal
Atrophic										
Severe.....	48	121	7.79	98	4.36	83	3.43	129	1.27	64
(Spondylitis) (1) ..	(14)	(42)	(8.36)	105	(4.43)	84	(3.93)	148	1.13	56
Atrophic Moderate....	27	48	7.61	96	4.92	93	2.69	101	1.83	92
Hypertrophic.....	52	71	7.51	94	4.73	90	2.78	105	1.70	85
Mixed.....	34	59	7.66	96	4.63	88	3.03	114	1.53	77
Syphilitic.....	5	11	7.66	96	4.54	86	3.12	117	1.45	75
Tuberculous.....	2	3	7.80	98	4.83	92	2.97	112	1.63	82
Gout.....	4	7	7.27	92	4.67	88	2.60	98	1.80	91
Miscellaneous										
Rheumatoid.....	5	6	7.89	99	5.05	96	2.84	107	1.78	90
* Non-Rheumatoid....	10	15	7.23	91	3.70	70	3.53	133	1.05	53
Normal.....	15	20	7.95	100	5.29	100	2.68	100	1.99	100

(1) Included in the Severe Atrophic Group.

\* Severely ill.

## DISCUSSION

Interpretation of these data requires some consideration of the factors which are known to play a rôle in the production of serum proteins. It is known that infection<sup>14</sup> or the presence of antigenic substances of various kinds,<sup>15</sup> may lead to an increase in the level of globulin fractions. The complicating influence of this factor in the present series must be considered in view of the fact that a large percentage of all the cases observed were at the time of examination, or had recently been, harboring demonstrable infective foci. It is also known that under conditions of chronic plasmaphoresis, infectious factors, and breakdown of tissue such as is involved in sterile abscesses, there may be interference with the production of albumin. This is also true of such apparently insignificant factors as the presence of viable yeast cells within the gastrointestinal tract.<sup>16</sup> Such agencies may in part account for some of the lower levels of albumin encountered. There is a possibility that albumin production may also be limited not infrequently by inadequate dietary supplies of the necessary amino-acids.<sup>17</sup> This rôle cannot be precisely evaluated in the present series on the basis of available data.

It appears from the figures here adduced that the several groups of chronic arthritics show a tendency toward a lowered albumin-globulin ratio (quotient). In terms of averages for the entire group as such, these differences are slight and might be regarded as within the normal range. However, reference to the figures representative of the several groups discussed suggests that the extent of deviation from normal parallels certain phases of the clinical condition. For example, the group of severe atrophic arthritics shows a low average ratio of 1.27, whereas the moderate atrophics show an average ratio of 1.83. It is also to be noted that the hypertrophic group shows a relatively low ratio of 1.70 as compared with the moderate atrophics. Further reference to individual cases, which are too numerous to cite here, provide additional support for this generalization.

It is interesting to observe the low ratio encountered in cases suffering from atrophic spondylitis (*spondylitis ossificans ligamentosa*). There is avowed difficulty in the mind of some students in accounting for the widespread calcification of the spinal ligaments in that variety of arthritis in which general atrophy and decalcification of osseous tissue are outstanding features. It is conceivable that the situation reflects influences emanating from the cord, and its associated roots, of either primary or secondary nature.

Upon the basis of the data presented indicating significant deviations from normal of serum protein fractions within all rheumatic groups and in the light of the aforementioned observations, certain therapeutic corollaries appear to be evident. Thus all agents which tend to stimulate globulin production should be removed; for example, infectious foci, not only because of their potential as atria of bacteria but also because the disintegration of tissue therein may give rise to products which may in turn act as antigens. Inasmuch as antigenic substances may arise from traumatized tissues, the protection of diseased articular tissues from mechanical trauma tends to diminish the amounts of "foreign" materials which, by entrance into the economy, stimulate globulin production and interfere with albumin production. Again, the provision of ample supplies of the raw materials necessary for the production of albumin is essential in terms of optimal nutrition. A combination of such measures at least approximates the conditions most favorable for a return toward the normal equilibrium of the patient in terms of protein metabolism. Such considerations have application to a wide variety of clinical conditions.

Another point worthy of mention in connection with the contrast presented by the atrophic spondylitics with an average ratio of 1.13 and the seriously ill non-rheumatoid group with a ratio of 1.05, is that such quotients do not fully reveal the significance of the analytical data. These quotients are derived by dividing the albumin concentration by the globulin concentration; viz.,  $4.43/3.93$  and  $3.70/3.53$  respectively. It is obvious that the albumin globulin ratio (quotient) derived from albumin 4.43 and globulin 3.93 would still be 1.13 even if the respective values were 2.21 and

1.96, despite the fact that in the second instance the albumin and the globulin levels are only one-half of the former and would, therefore, be associated with significantly different physiological influences. These considerations suggest the desirability of using a "series expression" for the total protein, albumin and globulin. For convenience of clinical interpretation this may be expressed in terms of the percentages of each fraction with respect to normal. The average values calculated on this basis are summarized in table 6. Obviously this is merely a short-hand expression

TABLE VI  
Contrast of Albumin-Globulin Ratios (Quotients) and Percentages of Normality

Type of Cases	Averages						
	A/G quotient	Series T; A; G			Series T; A; G Per cent of Normal		
Atrophic							
Severe.....	1.27	7.79	4.36	3.43	98	83	129
Spondylitis.....	1.13	8.36	4.43	3.93	105	84	148
Moderate.....	1.83	7.61	4.92	2.69	96	93	101
Hypertrophic.....	1.70	7.51	4.75	2.78	94	90	105
Non-Rheumatoid							
Severely ill.....	1.05	7.23	3.70	3.53	91	70	133
Normals.....	1.99	7.95	5.29	2.66	100	100	100

$A/G = \text{Quotient} \left( \frac{\text{Albumin (Gm. per 100 ml.)}}{\text{Globulin (Gm. per 100 ml.)}} \right)$

$T; A; G = \text{Total protein (gm. per 100 ml.); Albumin (gm. per 100 ml.); Globulin (gm. per 100 ml.)}$

$T; A; G \text{ per cent} = \frac{\text{Total protein}}{\text{Normal Total Prot.}} \times 100; \frac{\text{Albumin}}{\text{Normal Alb.}} \times 100; \frac{\text{Globulin}}{\text{Normal Globulin}} \times 100.$

and the value adopted as normal is as yet based upon too limited data to serve as a final standard. In spite of this short-coming such "series percentage" values may be utilized to advantage to indicate more clearly than heretofore the direction and approximately the extent of the deviation of the various protein fractions from the normal.

SUMMARY

A statistical analysis of the levels of total protein, albumin, globulin and the albumin-globulin ratios in the sera of patients with severe atrophic arthritis, atrophic spondylitis, moderate atrophic arthritis, hypertrophic arthritis, gout, tuberculous arthritis, syphilitic arthritis and a group of patients seriously ill with non-rheumatoid disease shows that slight changes occur with respect to the total protein levels in patients with rheumatoid disease. A significant number of severe atrophics, hypertrophics, and mixed cases shows a slight reduction in the albumin levels. Severe atrophics present increased levels of globulin and decreased albumin-globulin

ratios (quotients). Atrophic spondylitis is characterized by a higher level of total protein and a lower albumin-globulin ratio.

In order of mention, mixed cases, syphilitic, tuberculous, hypertrophics, miscellaneous rheumatoid, gouty and moderate atrophics show deviations from normal. It is to be noted that whereas the average albumin-globulin ratio in hypertrophics is not as low as among atrophics, it is significantly lower than is the ratio (quotient) of health. Furthermore, while only 7 per cent of the hypertrophics were below the lowest normal, 42 per cent of them were clustered around figures representative of the lowest levels of normality.

These data confirm the conclusion of Davis that atrophic arthritics often present low albumin-globulin quotients, and agree with the observations of Alred-Brown and Munro that hypertrophics frequently present ratios at or below lower levels of normality.

Expression of the levels of total protein, albumin and globulin as a series of numbers representative of the percentages of normal values respectively, is suggested as a mode of recording data on serum proteins. Such an expression avoids the possible error of apparent normality in the presence of abnormal albumin and globulin fractions.

The above data further support the view that therapeutic measures, including provision of an optimal supply and balance of nutrients, protection of inflamed or irritated tissue, removal of sources of toxemia and infection, are essential to any fundamental approach to arthritis, whatever the categorical type presented.

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# FACTORS INFLUENCING THE INCIDENCE AND COURSE OF OTITIS MEDIA IN SCARLET FEVER \*

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OTITIS *media suppurativa* is the most important complication in scarlet fever. Its importance is due to its frequency, to the possibility of permanent deafness, and to its relation to mastoiditis, sinus thrombosis, septicemia, petrositis, and meningitis.

At the outset, we must distinguish between the manifestations of the toxin, which consist of fever, vomiting, the enanthem and the rash, and those manifestations of the pus-forming properties of hemolytic streptococci, which may also give rise to fever. A middle ear abscess is one of several possible pyogenic complications in the course of the disease. Nor does this abscess materially differ in its course from that which occurs in measles, considered by most of us to be of virus origin. In scarlet fever, a culture made from the original discharge from the ear usually yields the hemolytic streptococci of scarlet fever,<sup>1</sup> while in measles a culture from the original discharge also yields hemolytic streptococci, but not of the scarlet fever variety. This same fact holds true for the majority of middle ear infections.<sup>2</sup> Furthermore, the incidence of middle ear involvement is much the same in measles as it is in scarlet fever, as we shall see later. Finally, it is important to bear in mind that the severity of otitis media in the course of scarlet fever varies quite as much as does the severity of the rash.

The middle ear may become inflamed without going on to suppuration. Seiferth's<sup>3</sup> observations suggest that such a simple inflammation is a common accompaniment of the eruptive stage as part of the enanthem. Indeed, I have observed this myself, but rather infrequently. However, I wish to report that while I was immunizing one child with small doses of the toxin, an earache promptly developed after three of these doses, which on examination showed redness of the drum. This child had had a simple inflammation in this same ear during a cold some four months previously. All this has to do with the eruptive stage of scarlet fever and emphasizes the possibility of the existence of a simple inflammation of the middle ear or possibly of the drum alone. However, such simple inflammation may also occur during convalescence, just as a middle ear abscess may form during the eruptive stage. Many of these simple cases have had paracenteses performed, and this artificial perforation brings them into the suppurative group because the terms perforative and suppurative are often

\* Presented at the New York meeting of the American College of Physicians, April 6, 1938. From the Department of Pediatrics, Harvard Medical School, and the Haynes Memorial, Massachusetts Memorial Hospitals. A synopsis of twelve unpublished articles dealing with this subject, based on a study of 10,000 cases of scarlet fever at the Haynes Memorial in conjunction with material gleaned from the literature.

used synonymously. This source of error in our attempts to analyze suppurative cases should be carefully kept in mind, especially when a hospital staff is zealous in incising the drum on the first symptoms of inflammation.

A middle ear abscess may occur at any time in the course of scarlet fever, but the majority of cases occur after the first week, and particularly between the fourteenth and the twenty-first day, which is the same period in which we find a peak for the other suppurative complications, as well as for the non-suppurative complications such as nephritis, arthritis, endocarditis, and purpura hemorrhagica. Furthermore, all these late complications, whether of a suppurative character or not, bear no relation to the severity of the original eruption.

In a review of reliable sources from the literature, I have accumulated 371,778 cases of scarlet fever in which the incidence of *otitis media suppurativa* is recorded (table 1); the average is 12 per cent. In a study of

TABLE I  
Incidence of Otitis Media in Scarlet Fever

	Total Scarlet Fever Cases	Developed Otitis Media	Otitis Media Per Cent
Metropolitan Asylums Board, London.....	258,160	32,121	12.4
All Other Available Sources (55) ..	113,618	14,222	12.5
Total.....	371,778	46,343	12.5
Haynes Memorial.....	9,840	1,202	12.2

10,000 cases on my own service, the incidence was also 12 per cent. Within the last few years, we find an incidence very close to 12 per cent reported from Stockholm,<sup>4</sup> Rome,<sup>5</sup> Boston,<sup>6</sup> and Los Angeles.<sup>7</sup> Thus climate, which plays an important rôle in the morbidity of scarlet fever, appears to exert no influence on the incidence per cent of middle ear involvement.

The incidence varies in different years, and this is often attributed to the *genus epidemicum* of scarlet fever. We can see in figure 1 how the *genus epidemicum* influences these fluctuations. I made up this chart from the reports of the Metropolitan Asylum Boards Hospitals of London from 1897 to 1914. You will note that the mortality rate is dropping throughout, in spite of wide fluctuations in the morbidity curve with a peak of 22,000 hospitalized cases in one year. The per cent of otitis media cases fluctuates, but not in relation to the morbidity curve of scarlet fever. The answer is to be found in the influence of season. During the peaks, the majority of cases of scarlet fever in these years occurred between July first and the last of November. This freak of the *genus epidemicum* accounts for the lowered incidence of otitis.

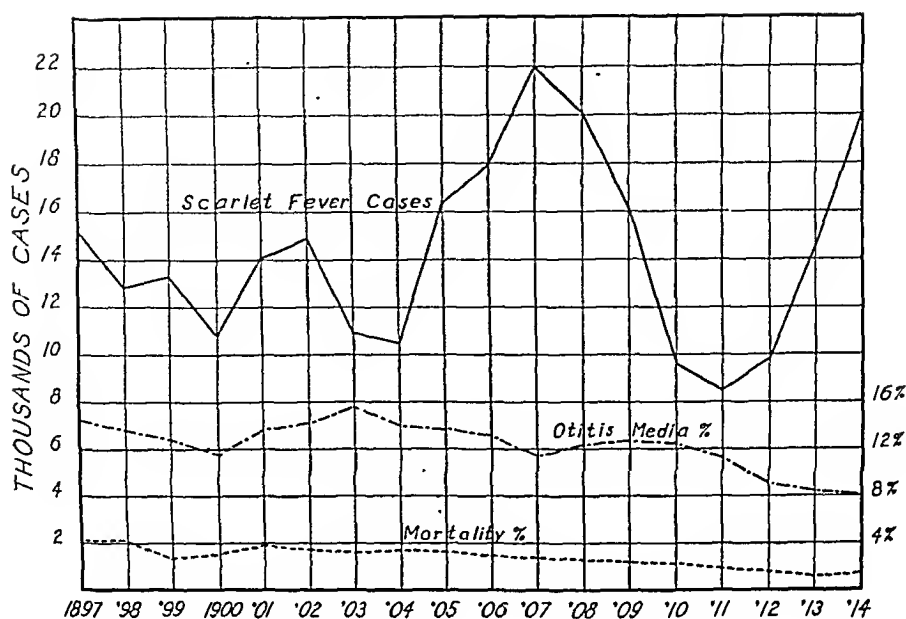


FIG. 1. Relation of morbidity and mortality to otitis media per cent. M. A. B. Hosp., London. 1897-1914.

I have arranged in figure 2 cases on my own service according to the months in which they occurred. You will see that there are fewer cases of scarlet fever in the summer and accordingly fewer cases of otitis. But the incidence of otitis media per cent—that is, the rate of otitis in relation

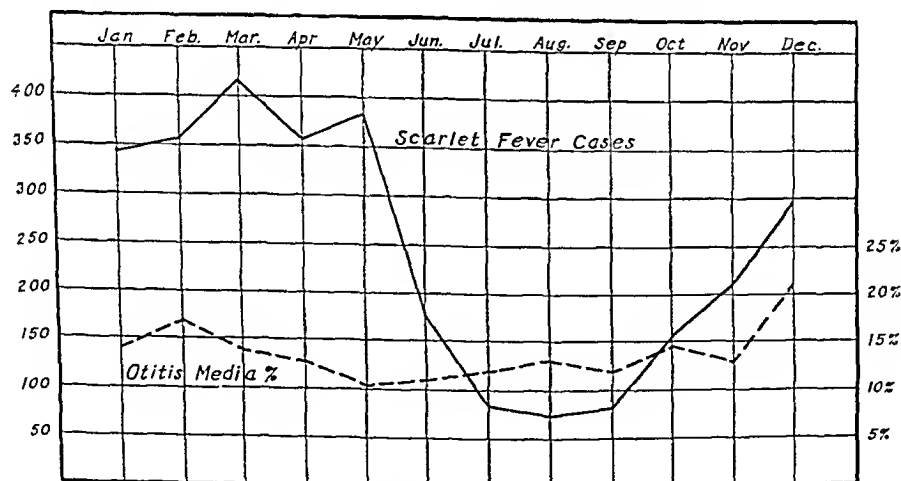


FIG. 2. Seasonal incidence of otitis media in scarlet fever. Haynes Memorial Hospital. Jan. 1928-Dec. 1932.

to the number of cases of scarlet fever—is lower during the summer months. This chart, like the preceding one, deals with the number of patients with otitis. If the otitis per cent were based on the number of ears involved, the curve would be more marked, because bilateral cases are more frequent in winter.

The age of the patient exerts a pronounced effect on the incidence of otitis media. Scarlet fever is infrequent in the first year of life, but when it does occur the incidence of otitis media is relatively high, but not so high as in the second and third years. On the whole, the otitis curve follows the mortality curve (figure 3) with the exception of the first years of life.<sup>8</sup> So essential is this age susceptibility to otitis media in the course of scarlet fever that we must bear it in mind in the evaluation of other factors whenever

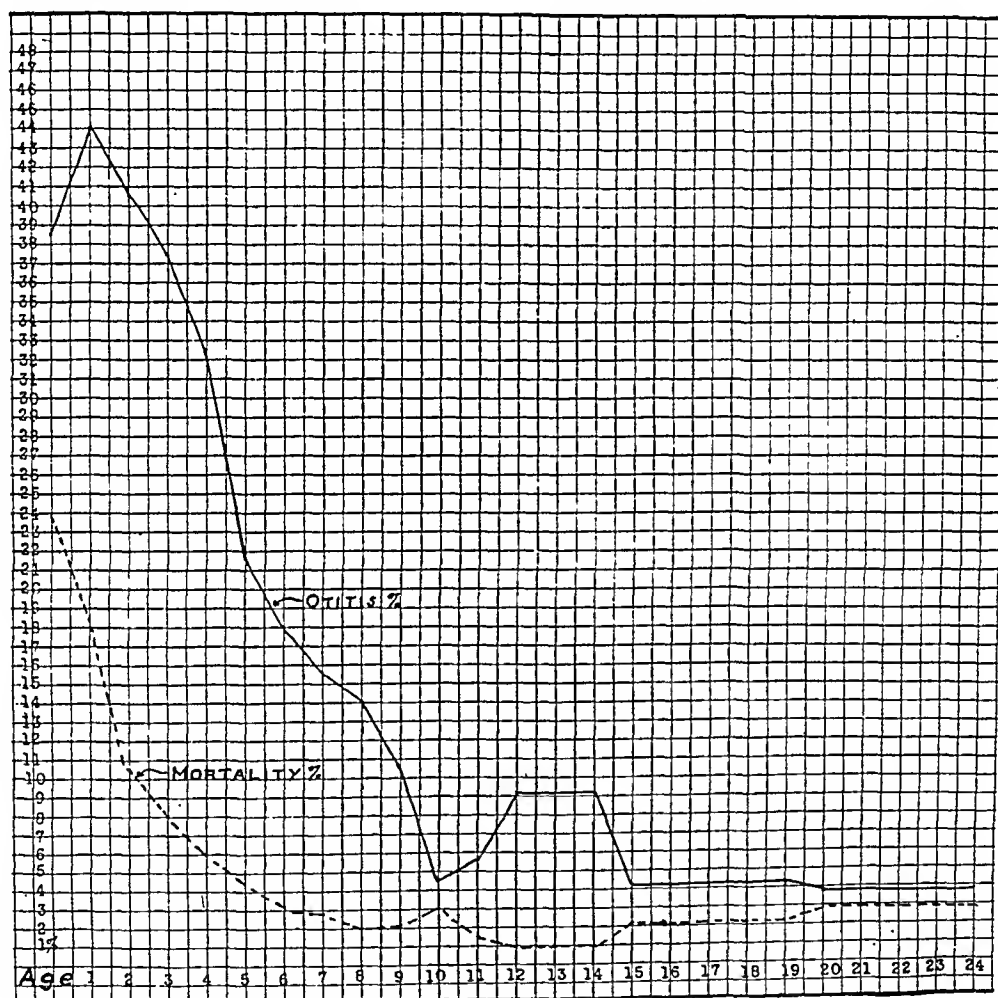


FIG. 3. Mortality per cent and otitis per cent in scarlet fever by age. Epidemic Hospital, Stockholm. 1901-1910. Ten thousand cases. (Holmgren.)

this is possible. You will see that in the second and third years of life, almost half of the cases develop suppurative middle ears. Furthermore, the incidence of bilateral cases is greater during the early years of life.

Figure 4 shows, in different age groups, the morbidity of scarlet fever beside the incidence per cent curve of otitis. This same peak that we observed in the previous chart is again in evidence as it is in charts emanating from Chicago,<sup>9</sup> Düsseldorf,<sup>10</sup> and Warsaw.<sup>11</sup> In other words, this peak is

always present and in this fact lies an interesting point which confutes a long-taught theory. If greater frequency of otitis in early life is dependent on the shortness and greater width of the Eustachian tube, why is the frequency less in the first year of life than in the second when the tube is growing longer and narrower? The vulnerability of the middle ear would seem to be less dependent on the length and width of the Eustachian tube than on other factors.

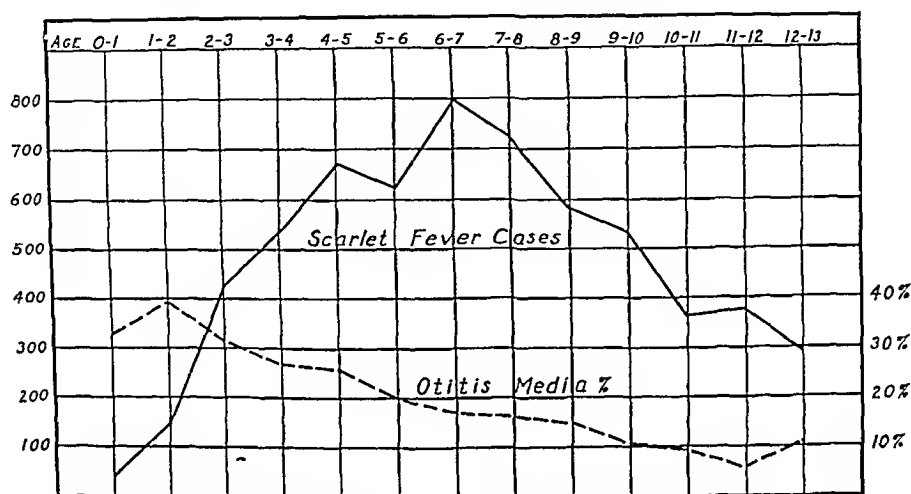


FIG. 4. Otitis media in scarlet fever by ages. Haynes Memorial Hospital. (Jan. 1914-Dec. 1932.)

Certain other infections superimposed on scarlet fever increase the incidence of otitis media. We should certainly expect this with common colds and this has been shown to be the case.<sup>12</sup> German measles and chickenpox, in combination with scarlet fever, do not raise the incidence. On the other hand, measles in the course of convalescence of scarlet fever, increases the likelihood markedly and diphtheria most of all. This is interesting because diphtheria by itself has a relatively low incidence of middle ear abscess—namely, 3 per cent. But diphtheria and scarlet fever in the same patient give an incidence as high as 65 per cent. Holmgren<sup>8</sup> found that even the presence of diphtheria bacilli in the form of carriers in scarlet fever patients augmented the incidence of middle ear involvement. This is a striking example of the enhancement of virulence of hemolytic streptococci through symbiosis.

In table 2 we see in the first column of figures the incidence of otitis in the common contagious diseases, and in the second column, the incidence when these diseases are in combination with scarlet fever. The enhancement of virulence through mixed infections could also be shown in the greater number of bilateral cases.<sup>11</sup>

Isolation of individual patients with scarlet fever (table 3) serves to protect them not only from the importation of mixed infections, but also from exposure to other strains of scarlet fever streptococci on the open ward.

TABLE II

Influence of Different Mixed Infections on the Incidence of Otitis Media Suppurativa

Disease Alone	Per Cent Otitis	In Combination with Scarlet Fever Per Cent Otitis
Scarlet Fever.....	12	
Measles.....	12	17-35
Diphtheria.....	3	31-65
German Measles.....	0	12
Chickenpox.....	0	12

TABLE III

Isolation of Scarlet Fever Cases in Separate Cubicles Lowers the Incidence of Otitis Media Suppurativa

London 1904 (Caiger).....	6.3%
Stockholm 1931 (Lichtenstein).....	4.6%
New York 1937 (Stimson).....	6.8%

Such exposure increases the incidence of otitis media, as is shown by figures from London,<sup>13</sup> Stockholm,<sup>14a</sup> and more recently by Stimson<sup>25</sup> at the Willard Parker Hospital here in New York. This is an indictment of the open ward treatment of scarlet fever, and yet in Stockholm where hospitalization<sup>14b</sup> of scarlet fever is required by law, it has been shown that the mortality has been substantially reduced by hospital care, even with the open ward.

Tonsillectomy has been shown by Kaiser<sup>15</sup> (table 4) to reduce materially the incidence of scarlet fever. Three per cent of the tonsillectomized chil-

TABLE IV

Influence of Tonsillectomy on Incidence of Scarlet Fever  
(Kaiser)

Based on a Control Study of 4,400 Children over a Ten-Year Period

Scarlet Fever Occurred in Tonsillectomized.....	3.3
Scarlet Fever Occurred in Those with Tonsils.....	4.6

dren came down with scarlet fever in contrast to 4 per cent among those whose tonsils were not removed. This, of course, may be and probably should be looked upon as a difference of 25 per cent which is well worth while.

Bradford<sup>16</sup> went on to study the effect of these tonsillectomies on persons who later contracted scarlet fever. He found that those without tonsils had slightly less suppurative middle ears than those in whom the tonsils were present. The observations of Hofmann<sup>17</sup> and Nordwall<sup>18</sup> fail to substantiate Bradford's results. All three of these observers (table 5) have taken into consideration the age of the patients, but only in Nordwall's series is the age in the two groups equalized by selection. The figures in the totals favor those who had tonsils.

TABLE V

Influence of Previous Tonsillectomy on Incidence of Otitis Media in Scarlet Fever

	Without Tonsils on Admission	Otitis media		With Tonsils on Admission	Otitis media	
		Cases	Per cent		Cases	Per cent
Hofmann, 1931.....	54	10	18.5	1,264	141	11.5
Bradford, 1932.....	107	27	25.2	426	117	27.4
Nordwall, 1934.....	104	20	19.2	312	45	14.4
Totals.....	265	57	21.5	2,002	303	15.1

In my own series (table 6) where the age factor has governed the selection of controls over the same period, it appears that the previous removal of tonsils—and presumably of adenoids—exerted no beneficial influence on the incidence of middle ear abscess or mastoiditis. It should be kept in mind that these two hundred children had had their tonsils removed because their tonsils were defective, at least we hope so, and that they might have had more serious troubles when they succumbed to scarlet fever if these defective tonsils had not been previously removed. The significance of this speculation is of importance in drawing conclusions from the data presented here.

TABLE VI

Influence of Previous Tonsillectomy on Incidence of Otitis Media in Scarlet Fever, Haynes Memorial Hospital, 1930-1938. Equalized Age Groups from 5 to 15, Equal Seasonal Groups, Mixed Infections Omitted

	Cases	Suppurative Otitis Media Per Cent	Surgical Mastoiditis Per Cent
Without Tonsils on Admission.....	200	13.5	5.5
With Tonsils on Admission.....	1,000	12.0	4.1

The value of tonsillectomy during the convalescence of scarlet fever is an entirely different matter. This subject has not been studied with sufficient care to warrant bringing before you any statistics, but the practice of removing very large and diseased tonsils after the third week is now well established as a safe procedure, which often appears to have a salutary influence on the course of suppurating ears, as well as on other complications. The objections are usually from those who have had no experience with this procedure.

The influence of paracentesis on the course of otitis media is not so great as one would expect from the textbooks. That paracentesis is of value for the relief of pain, for the release of pressure behind a bulging drum, or when an inadequate opening exists is obvious. But whether para-



centesis reduces the length of time of suppuration is not a simple matter to decide. Proof of this has been attempted <sup>6</sup> but not in a convincing manner. What we are all interested in is whether paracentesis prevents extension of the suppurative process into the mastoid cells. Kopetzky <sup>19</sup> has recently brought the level of this discussion to a higher plane. Most of the literature on this subject consists of poorly controlled data, unconsciously manipulated to defend the value of incising the drum. Since a corollary to this theory is the earliest possible incision, many simple cases, which would never have gone on to suppuration anyway, have been incised unnecessarily and this has swelled the favorable results on the paracentesis side of the column.

It has remained for Williams <sup>20</sup> to present us with results in a study of 29,298 cases of scarlet fever, which are of particular value, because the two columns are practically equal. Even in this series, we must bear in mind that probably a number of drums were incised which never would have gone on to suppuration, and therefore should never have been classed as suppurative cases.

We have here (table 7) a summary of his figures. Since every patient has two ears, he deals with the number of ears involved. We have prac-

TABLE VII

Otitis Media in Scarlet Fever; Incidence of Surgical Mastoiditis in Relation to Paracentesis. Based on Results in 29,248 Cases of Scarlet Fever, Philadelphia Hospital for Contagious Diseases. (By Permission of Horace J. Williams, M.D.)

	Number of Ears	Number of Mastoids	Per Cent Mastoids	Number of Bil. Mastoids
Spontaneous Rupture . . . . .	1,843	236	12.8	46
Paracentesis before Rupture . . . . .	1,852	194	10.4	45
Paracentesis after Rupture . . . . .	415	27	6.5	1

tically an equal number of spontaneously ruptured drums and drums which were incised previous to rupture. For each of these groups, there is an almost equal number of bilateral mastoids, and this fact suggests an equality in virulence in the two groups. The difference in mastoiditis in the two groups is that between 12.8 and 10.4.

If we manipulate the remaining 415 cases, which ruptured spontaneously and were then incised, we can bring the two figures even nearer by adding them to the spontaneously ruptured group, where they naturally belong, unless we prefer to infer that incision after rupture is the best method, which is nonsense. The discrepancy in this last group lies in the fact that there should have been at least ten bilaterals, proving that this group comprised a milder type of virulence. For this reason alone, we should not add them to either group, because the value of Williams's series lies in the fact that we have two equal numbers of ears with equal numbers of bilaterals, the most outstanding data on record. The difference between 12.8 and 10.4

must be discounted by the speculation that a number of drums were incised that never would have ruptured if left alone.

The value of recognizing and operating on suppurative mastoids in the course of scarlet fever is of the utmost importance. It saves the hearing, shortens the period of isolation, and saves lives. Gowen<sup>21</sup> attempts to demonstrate the value of paracentesis by extolling the virtues of an intern who, he says, was so skilled in this art that only three surgical mastoids developed on his three months' service, while in the period of 10 days after his transfer, four mastoids developed. I am tempted to praise the second intern, who probably found the mastoids that were missed on the previous service. In other words, I believe that the recognition of surgical mastoiditis is of infinitely greater importance to the patient than early paracentesis.

The influence of early serum treatment on the incidence of suppurative otitis media is another field for heated discussion, because here again opinions run strong and there are innumerable pitfalls in the presentation of evidence.

We have in table 8 a summary of the results of observers who have made an effort to consider the various factors involved. The answer is in favor of the early use of serum, but with reservations, which I cannot go into here.

Lichtenstein<sup>14c</sup> gives us some very valuable observations (table 9) because they include only those otitis cases which developed after the first week. You will notice that in the cases not treated with serum, there were more cases of otitis, but fewer mastoids. So here again we should try to be as careful in our observations and conclusions as is the Professor of Pediatrics in Stockholm.

Cod liver oil has been frequently recommended as a preventive of middle ear complications, but on the scarlet fever wards of the Boston City hospital<sup>22</sup> large doses of cod liver oil concentrate administered to 500 cases failed to reveal any significant benefit in this respect. The same negative results have also been recorded from the administration of vitamin A in the form of carotene.<sup>23</sup>

The influence of sulphanilamide on the incidence of otitis media is difficult to evaluate because of the lack of material. However, Peters and Havard<sup>24</sup> in London have recently reported on 150 cases treated with this drug and well controlled by 150 cases treated in the usual manner. The incidence of otitis and mastoiditis was the same in both groups. In my own investigations,\* which you see here, the factors of age and season are covered as closely as possible. The usual dose for the age was administered by mouth during the febrile stage. The results (table 10) in this small series suggest a possible beneficial action on the part of the drug in preventing suppurative otitis media. There is no evidence that it prevented mastoiditis. The question will be raised whether the drug would not have

\* Sulphanilamide was used in this series in the form of prontosil supplied through the courtesy of the Winthrop Chemical Company.

TABLE VIII

Results of Serum Treatment of Scarlet Fever on Incidence of Otitis Media

Author	Date	Ref.	Serum Control	Cases	Otitis Media	Otitis Media Per Cent
Dick Chicago	1925	26	Serum Control	50 50	3 8	6.0 16.0
Gordon Chicago	1927	27	Serum Control	317 367	22 44	7.0 12.0
Doolittle Seattle	1927	36	Serum Control	100 100	6 5	6.0 5.0
Prinzling Germany	1928	28	Serum Control	97 185	9 20	9.3 10.8
Toomey Cleveland	1928	29	Serum Control	283 60	26 9	9.1 15.0
Craig Scotland	1928	30	Serum Control	500 500	40 54	8.0 10.8
Scott Liverpool	1928	37	Serum Control	150 240	17 24	11.0 10.0
Place Boston	1929	31	Serum Control	132 668	12 73	9.0 11.0
Lichtenstein Stockholm	1931	14 b	Serum Control	700 350	68 46	9.7 13.1
Winkel Germany	1932	38	Serum Control	266 132	55 24	20.6 18.0
Hunt Chicago	1933	39	Serum Control	882 1,421	54 219	6.1 15.4
Hauf Germany	1933	32	Serum Control	124 124	22 23	17.7 18.5
Stevenson et al. Ohio	1933	33	Serum Control	112 84	8 14	7.3 17.1
Lucchesi et al. Philadelphia	1934	34	Serum Control	3,045 2,332	225 229	7.39 9.83
Hoyne et al. Chicago	1935	35	Serum Control	1,930 6,282	196 854	10.15 13.6
Wesselhoeft Boston	1938		Serum Control	549 1,647	53 207	9.6 12.6
TOTALS			SERUM CONTROL	9,237 14,542	816 1,853	8.8 12.7

N. B., some authors give only the otitis media per cent; thus the number of cases of otitis media has to be supplied. The day of the administration of the serum is an important factor.

TABLE IX

Epidemic Hospital, Stockholm, 1926-1929. A. Lichtenstein. Complications after First Week of Scarlet Fever with and without Serum

	Cases	Otitis	Mastoiditis
Antitoxin Serum.....	350	30	9
Convalescent Serum.....	350	38	10
No Serum.....	350	46	8

Age, Season and Sex Equal in the Three Groups.

TABLE X

Haynes Memorial Hospital, Boston, 1936-1937. Scarlet Fever Cases without Complications on Admission. 100 Cases Treated with Prontylin during Febrile Stage, 100 Selected Control Cases over Same Period without Prontylin, Average Age  $10\frac{1}{2}$  in Each Group

	No. of Cases	No. of Cases Developing Otitis Media	Bilateral Otitis Media	No. of Cases Developing Mastoids	Bilateral Mastoids
Prontylin Group.....	100	6	4	2	1
Control Group.....	100	15	6	3	1

Note: In the selection of the control cases alternating admissions were used as closely as possible but the main attempt was to select a series of cases of equal average severity on admission and of equal average age.

had a better chance to be of benefit if continued longer. One of the prontylin-treated cases developed later a bilateral mastoiditis and septicemia with a positive blood culture of hemolytic streptococci, yet this was one of our five scarlet fever cases with positive blood findings last year to recover under strenuous prontylin therapy. This experience in septicemia is very encouraging, but further hospital investigations are necessary before we can say that the drug is effective in the prevention of aural complications in scarlet fever.\*

### SUMMARY

1. The incidence of suppurative otitis media in scarlet fever has been about 12 per cent.
2. The age of the patient exerts a profound influence on the frequency of this complication, its incidence being about 40 per cent in the first years of life.
3. Otitis media is more frequent in winter than in summer.
4. Diphtheria and measles when in combination with scarlet fever augment the frequency of otitis media.
5. Isolation lowers the incidence.
6. While a previous tonsillectomy reduces the likelihood of scarlet fever, the absence of tonsils cannot be shown to lower the incidence of otitis media.

\* Since this paper was read the following has been published: WESSELHOEFT, C., and SMITH, E. C. The use of sulfanilamide in scarlet fever, New England Jr. Med., 1938, ccxix, 947.

7. Paracentesis does not materially reduce the incidence of surgical mastoiditis.

8. Early serum treatment appears to have a favorable effect on the incidence of otitis media.

9. The administration of cod liver oil concentrates to scarlet fever patients does not materially lower the incidence of otitis media.

10. While the administration of sulphanilamide appears to be of distinct value in the event of septicemia, further hospital investigations are necessary before this drug should be recommended as a routine prophylactic measure for the aural complications of scarlet fever.

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# NON-GRANULOMATOUS CHRONIC ENTERITIS\*

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THE diagnostic study of patients whose symptoms suggest intrinsic disease of the gastrointestinal tract is too often limited to a careful study of the esophagus, stomach, first portion of the duodenum, and colon. If the clinical picture is suggestive, an attempt is made to demonstrate the presence or absence of a tumor of the small intestine or of a non-specific granuloma (regional enteritis, terminal ileitis). But usually only the most cursory observation of the rest of the small intestine is made, incidental to the examination of the six-hour film, when the small bowel is frequently empty. Because of the failure to include a detailed study of the small intestine in the routine investigation of the gastrointestinal tract, the underlying cause of the symptoms of many patients, who have definite disturbances of the small bowel, is undiagnosed or wrongly attributed to a neurosis.

The milder, non-granulomatous, chronic inflammatory changes of the small intestine have received but scant attention. The situation with respect to this entity is not unlike that which existed with regard to chronic gastritis until a few years ago. The scarcity of pathological studies, the failure to properly evaluate the symptoms produced by these conditions, and the lack of a suitable diagnostic technic, which, in the case of gastritis, has been supplied by the flexible gastroscope, rugal studies; etc., have caused these conditions to remain undiagnosed.

However, Porges,<sup>5</sup> attempted to establish a clinical basis for their recognition. We believe that mild, chronic inflammatory enteritis, of non-granulomatous nature, occurs with great frequency and causes recognizable subjective and objective findings. The changes which occur in the small bowel in sprue have been described. There are, however, many patients who have no diarrhea, who may even be constipated, and who show no definite evidence of vitamin deficiency whose symptoms are due to chronic inflammatory changes in the small bowel.

## PATHOLOGY

Pathological studies of chronic enteritis are very few, for the disease is not surgical and does not have a fatal outcome. In the older writings, we find rare descriptions of autopsy material where the cause of death was extra-intestinal. In view of the pre- and postmortem changes which occur in the gastrointestinal tract, the value of these findings is limited. Infiltration of the intestinal wall, of the mucosa and the muscularis are de-

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scribed; in later stages atrophy of the glands and changes in the lymphatics and nerve endings have been seen (Nothnagel,<sup>3</sup> Schmidt,<sup>7</sup> Siegmund<sup>8</sup>).

In connection with our cases associated with alcoholism, it is interesting to note that a French pathologist, Ribadeau Dumas,<sup>6</sup> described characteristic changes of the small intestine in cases of chronic alcoholism similar to those found in the stomach. He observed edema and swelling of the mucosa, a spotty and streaky pigmentation, fatty degeneration of the mucosal glands, hemorrhagic erosions, and scar formations; in more severe cases, fibrosis of the intestinal wall. In sprue and pellagra ulcerative lesions have been described.

### DIAGNOSIS

The diagnosis of chronic non-granulomatous enteritis is based on: (1) the history; (2) localized tenderness; (3) stool examination; (4) roentgen-ray findings.

1. *History*: The patient complains of a feeling of heaviness and distention in the abdomen. He is nauseated within a few hours after meals, and is aware of splashing, gurgling noises in his abdomen. There is a sense of abdominal unrest due to pain which varies in intensity from mild to cramp-like sensations, often localized in the umbilical region. Poor appetite is a frequent, but not constant, symptom. Increased gas formation and flatulence are most common. Eructations and heartburn, when present, may be due to a coexistent gastritis. While constipation is frequent, the bowel movements may be regular, and occasionally there may even be a diarrhea, if the fat or roughage intake is excessive.

It is a fairly common occurrence to find that a patient, in whom evidence of an enteritis is found, has for years been regarded as a neurotic, or else that he has been treated for ulcer, gastritis, chronic appendicitis, or colitis. Some of these patients have mild syncopal seizures or experience vertigo, often one to three hours after meals, probably due to mesenteric irritation induced by overactivity of the small bowel. Vasomotor rhinitis occurs, as do neuritic and arthritic pains.

2. *Tenderness* is usually found to the left of the umbilicus. At times there may be tenderness to the right and slightly above McBurney's point, when the ileum is chiefly involved.

3. *Stools* are usually formed and contain large amounts of fatty acids and soaps. In evaluating this finding, it is important that the total daily intake of fat has not exceeded 80 grams, because if larger amounts of fat are taken even by a normal individual there will be a certain amount of unabsorbed fat in the stool. It is also necessary to rule out the presence of pancreatic disease, but in the latter case stools are characteristically more bulky and the fat is chiefly in the form of unsplit, neutral fat. The disturbed function of the small intestine causes incomplete digestion not only of fats but also of carbohydrates and proteins. The latter two undergo bacterial decomposition in the distal small intestine and in the colon, thus



giving rise to the excessive gas production and the resulting flatulence. Occasionally one may see undigested starch granules or muscle fibers in the stool. The urine usually shows an increased indican reaction.

4. *Roentgen-ray examination* reveals two types of chronic enteritis, hypermotile and hypomotile. In either case, there may be irregular, smudged filling of the coils, and deep spasms and peristaltic contractions may be seen. Instead of the smooth, continuous filling normally observed, isolated coils are found, and there are variations in the contours and caliber of the intestinal segments. Dilated as well as narrow loops are seen. The mucosal pattern shows thickening of the markings. Frequently there are evidences of increased fluid and gas content.

A standard technic must be followed in examining the small intestine. The stomach must be empty. A thick mixture of four to five ounces (120 to 150 c.c.) of barium sulphate in water is administered. Observations, fluoroscopic and radiographic, are made immediately, and one-half hour after the administration of the barium mixture, and thereafter at one or two hour intervals, depending upon the rapidity of the progress of the meal, until the small intestine is empty. It is important that only a water-barium meal be given. Normally this produces a smooth filling of the intestinal loops, whereas the addition of a fatty substance produces a smudged, intermittent filling of the loops even in a healthy individual.

Normally at two hours after the meal, there is either no barium or a very slight amount of barium in the cecum. If, at two hours or sooner, there is a considerable amount of barium in the cecum and colon, hypermotility of the small intestine is demonstrated.

The normal small intestine is completely empty in a maximum of eight hours after the meal is given. If it requires more than eight hours to empty the small intestine, hypomotility is present.

Both deviations from the normal, hyper- and hypo-motility, in a patient with normal gastric motility indicate the presence of a functional or organic disorder of the small bowel.

It is necessary to exclude the effect of drugs before interpreting the small intestinal picture. For example: a saline laxative may change the intestinal pattern and increase the motility. Morphine, on the other hand, has been shown by Pendergrass<sup>4</sup> to produce delayed motility and gas in the small intestine for 24 hours and sometimes for as long as five days. Also, extra-intestinal factors, such as thyroid disease, jaundice, and emotional disturbances, must be considered in evaluating the motility of the small bowel.

The following cases illustrate the two types of chronic enteritis.

#### CASE HISTORIES

*Case 1.* S. F., a 34 year old white female, complained for 10 years of epigastric distress, bloating and distention, one to two hours after meals; appetite poor, gradual loss of weight from 118 lbs. to 109 lbs.; sick feeling and bad taste, tongue coated, constipation; frequent pain in the umbilical region. Distention was so marked in

the afternoon that she could not wear a corset. There was an occasional syncopal seizure at the height of her distress. She had a bowel movement twice a week. There was a marked inferiority complex as a result of her symptoms.

*Physical examination:* Acne of face and chest. Tongue coated. Blood pressure 110 systolic and 75 diastolic. Abdomen slightly distended and tympanitic. There was a point of tenderness to the left of the umbilicus and also above McBurney's point. Rectal examination and proctoscopy negative.

*Laboratory data:* Gastric analysis after Ewald test meal: free acid 28, total acidity 42. Blood count; hemoglobin 95 per cent, red blood cells 5,100,000. Urine

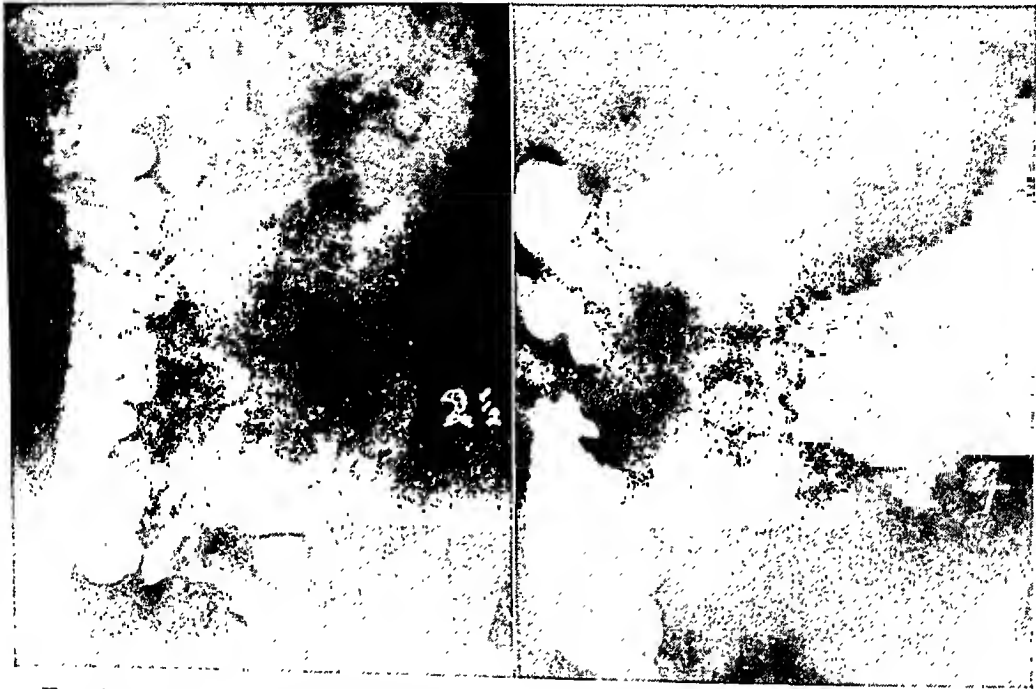


FIG. 1. Hypermotile enteritis;  $2\frac{1}{2}$  hours p.c., stomach empty, colon filled from cecum to splenic flexure; jejunal coils dilated, irregular contours, patchy filling; ileum, varying caliber of loops, spastic contractions, with dilatation above, thickening of mucosal pattern; 4 hours p.c., small intestine almost empty, deep haustration of colon, which is filled to splenic flexure.

examination negative. Stool segmented, negative for blood; microscopically, large amounts of fatty soaps as crystals and globules, and of fatty acids, no mucus, occasional muscle fiber, no starch.

*Röntgen-ray:* Stomach moderately ptotic, active peristalsis, normal triangular duodenal cap, marked hypermotility of small intestine and signs of enteritis (figure 1).

*Diagnosis:* Hypermotile enteritis.

*Case 2.* W. M., a 53 year old, white male, a professional bridge player, complained for several years of a continuous bloated and heavy feeling in the abdomen, most marked two to three hours after meals, when he felt compelled to open his trousers because of the distention. He felt relieved after passing flatus. He drank excessively of alcoholic liquors. He was constipated, usually three to four days at a time. His appetite was good. There was occasional belching. For the past year he had had a vasomotor rhinitis which was not present when his abdominal symptoms were not active. He also had generalized aches and pains.

*Physical examination:* Weight 130 lbs.; blood pressure 115 systolic and 60 diastolic. Generally hypersensitive. Heart negative; the lungs showed a basal bronchitis. Abdomen distended, slightly tympanitic, no tenderness. Extremities and reflexes normal. Tenderness over sciatic nerves.

*Laboratory data:* Urine showed indican 3 plus, otherwise negative. Gastric contents: normal acidity, no blood. Stool was hard, constipated with large amounts of unabsorbed fatty soaps and acids, occasional muscle fiber, no starch.

*Roentgen-ray:* Stomach normal. Marked hypomotility of small intestine and signs of enteritis (figure 2).

*Diagnosis:* Hypomotile enteritis in an alcoholic.

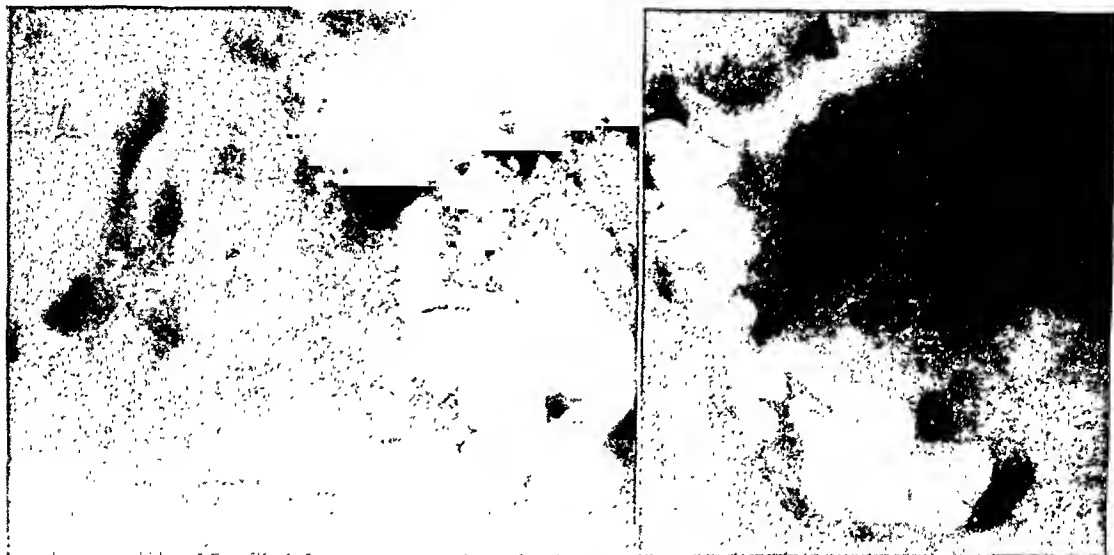


FIG. 2. Hypomotile enteritis; in alcoholism:  $2\frac{1}{2}$  hours p.c., small amount of barium in stomach, diffuse filling of jejunum, varying width of coils, patchy filling, thickening of pattern; 8 hours p.c., large amount of barium in atonic wide ileum.

### RELATION TO VITAMIN DEFICIENCY

In the hypermotile type of chronic enteritis, the finding of undigested fat in the stool is easily explained by the rapid passage through the small bowel.<sup>1</sup> But in the hypomotile group, another explanation must be sought, for although the food mixture is in longer contact than normally with the small intestinal mucosa, the same evidence of impaired fat digestion and absorption is found. Verzar<sup>10</sup> offers an experimental basis for the pathology of absorption in the small intestine. He produced a vitamin B deficiency in animals and showed that it was accompanied by a disturbance in absorption of carbohydrates and fats. In animals in whom the adrenal cortex was removed a similar disturbance resulted. This could be corrected by supplying adequate amounts of vitamin B or of cortical hormone as the case might be. Clinically, however, little is known of the pathology of absorption in the small bowel. It is likely that sprue, in which the presence of small intestinal hypomotility, along with severe diarrhea, has been demonstrated by Mackie, Miller and Rhoads<sup>2</sup> and by Snell and Camp,<sup>9</sup> belongs in this category. The improvement in the appearance of the small intestine which these authors have been able to produce by the administration of liver extract has led us to give liver extract parenterally to our cases of enteritis, often with great improvement clinically and roentgenologically, especially in the hypomotile form.

Clinical experience also points to a close relationship between hypomotile chronic enteritis and the deficiency diseases. We often see this form of enteritis in conditions which lead to vitamin deficiency, either through failure of intake or failure of absorption. Thus chronic enteritis may be seen in association with ulcerative colitis (figure 3), in chronic alcoholism (case 2) and in patients who have been on restricted, low vitamin diets for a long period of time. Such cases are seen where, due to persistence of symptoms after gastric operations, a very restricted diet has been taken for months or years (figure 4).

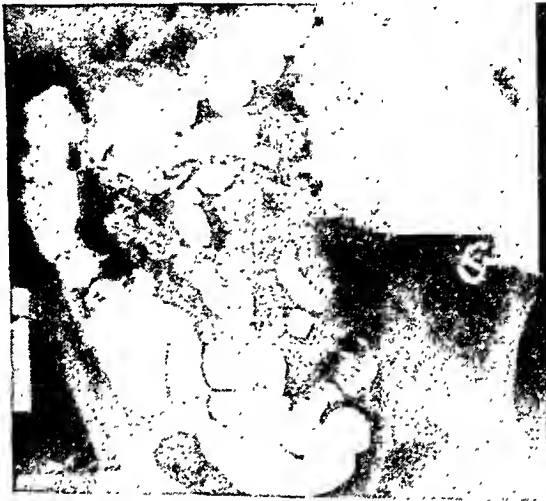


FIG. 3. Hypomotile enteritis with ulcerative colitis. 6 hours p.c., large amounts of barium in ileum, spasms and dilatation, smudged pattern due to hypersecretion; [8 hours p.c., the distal ileum was filled].

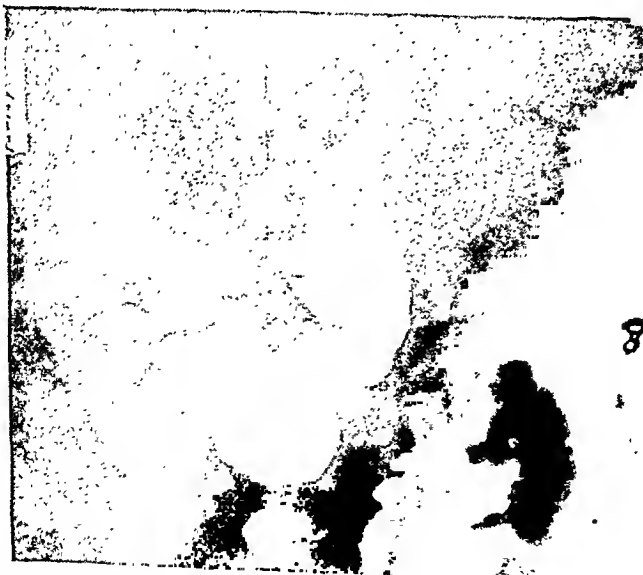


FIG. 4. Hypomotile enteritis following gastro-enterostomy. 8 hours p.c., hypersecretion, segmentations, spastic contractions and marked dilatation of ileum, isolated loops.

## THERAPY

Treatment of chronic enteritis is dietetic and medical. A light, bland, cellulose-poor diet is given, in which vegetables and fruits are taken only as juices. Tender meats, finer cereals and starches and moderate amounts of fat are permitted. The medical treatment consists of mild astringents, such as bismuth subgallate, colloidal aluminum hydroxide preparations, etc. We give liver extract by injection, particularly in the hypomotile group, and also supply vitamins in large quantities, especially vitamin B, which is given parenterally because of the impaired absorption from the intestine. With this regime, we have had good results, many times in patients in whom symptoms had persisted for years in spite of numerous therapeutic efforts. On the other hand, it should be stressed that there is a great tendency to recurrence of symptoms when treatment is suspended. In this respect the disease resembles other chronic inflammatory disturbances of the gastrointestinal tract.

## SUMMARY

The history, physical examination, stool microscopy, and roentgen-ray findings furnish sufficient criteria for the clinical diagnosis of chronic non-granulomatous enteritis. This form of enteritis may occur alone or in association with gastritis and colitis. It is frequently observed following gastric operations and as a residuum of acute intestinal disorders, and seems to be related to vitamin deficiency.

Careful small intestinal study of patients with unexplained digestive disturbances will often reveal a chronic enteritis as their cause.

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# THROMBO-ANGIITIS OBLITERANS ASSOCIATED WITH DIABETES MELLITUS\*

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THOUGH thrombo-angiitis obliterans is a comparatively rare disease, the association of this condition with diabetes mellitus is still rarer. Only seven cases, as revealed by a search of the literature, have been reported. Five of these have been seen at The Mayo Clinic, Adams<sup>1</sup> having reported one in 1930 and one of us (Horton) and Allan<sup>2</sup> four in 1934. The other two cases were reported by Davidson<sup>3</sup> and Delbet,<sup>4</sup> respectively, but although both patients were males, the diagnosis in both cases, from the standpoint of the occlusive arterial disease, was questionable.

Davidson's patient was 65 years of age when first seen. Phlebitis occurred postoperatively. No information was available as to the presence or absence of calcification of the vessels, but the oscillometer indicated poor circulation even to above the level of the middle third of both thighs, where normal circulation was gradually approached, the left leg being more involved than the right. Delbet's patient was 61 years old and, in addition to diabetes, had syphilis. Delbet's paper gave an excellent description of thrombo-angiitis obliterans, but aside from this there was no reference to the patient's condition. As has been said, therefore, the clinical evidence was not adequate in either case to establish the diagnosis.

Bernhard,<sup>5</sup> in a study of the chemical constituents of the blood in thrombo-angiitis obliterans, found a few cases in which there was a high value for blood sugar (up to 210 mg. per 100 c.c.) and a low glucose tolerance; specific reference to the condition other than this was not made.

The present report is of five additional cases of thrombo-angiitis obliterans associated with diabetes which have been encountered at The Mayo Clinic from the latter part of 1932 up to December 1937. About the five patients previously seen at the clinic, the following additional information has been obtained: Adams' patient and Horton and Allan's patient in case 3 have not responded to our follow-up letters. The patient in case 1 of their report is dead as therein recorded, but the patients in cases 2 and 4 are still in good condition, their diabetes being very mild and the obliterative process well compensated for. The patient in Horton and Allan's case 2 has had no symptoms for four years and is not on a restricted diet.

## REPORT OF CASES

*Case 1.* This patient, of Jewish descent, was 47 years of age at the time of his registration at the clinic on September 29, 1931. For two years, he had had intermittent claudication pain in his left leg and foot after walking six to eight blocks.

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Episodes of numbness and coldness of both feet, chiefly the left, with occasional rest pain had been noted since November 1930. There was no history of phlebitis or ulcer. The patient had smoked 20 cigarettes a day for the previous five years. The presence of the diabetes had been discovered in 1929, the value for blood sugar then being 166 mg. per 100 c.c., but it had been easily controlled by insulin and diet.

On the patient's admission to the clinic, the value for blood sugar was 120 mg. per 100 c.c.; there was no sugar in the urine and other laboratory tests gave negative results. Slight calcification of the arteries about the right ankle was revealed in a roentgenogram. Postural changes in color consisted of pallor of grade 3 of the left and of grade 1 of the right foot on elevation, whereas when dependent the left foot exhibited rubor, of grade 3, with very slow filling, and the right, rubor of grade 1. The left popliteal, dorsalis pedis, and posterior tibial vessels were occluded, but there was a grade 1 pulsation in the right posterior tibial artery. Arterial pulsations in the hands and arms and right leg were otherwise normal except in the right dorsalis pedis artery in which they were graded 3 to 4. Some improvement was noted in the circulation of the left leg following medical treatment which consisted chiefly of typhoid vaccine, contrast baths, postural exercises, use of a baker, and the cessation of smoking.

The patient returned to the clinic on August 10, 1933, complaining of claudication pain in his left leg after walking 100 feet and of a burning sensation in this leg when it was dependent for 15 minutes. Postural changes in color, however, were now somewhat less marked in this left foot, pallor being graded 1 to 2 on elevation, and rubor graded 2 on dependency; color returned partially in 15 seconds and completely in 50 seconds. Changes in color were absent in the right foot. Pulsations in the vessels of the legs were the same as at the previous examination except that the right posterior tibial artery was practically completely occluded. The ulnar arteries, however, were open, grade 2. Roentgenograms of the left leg did not reveal calcification of the vessels. The value for blood sugar was 178 mg. per 100 c.c. The test for sugar in the urine gave a negative result because of a high renal threshold. With the glucose tolerance test, the value for blood sugar rose to 261 mg., 357 mg., and 244 mg. per 100 c.c. at the end of the first, second and third hours, respectively, with corresponding values for sugar in the urine of 0.9 gm. (1.94 per cent), 3.47 gm. (2.70 per cent), and 2.79 gm. (2.87 per cent). The diabetes was well controlled by a diet consisting of 101 gm. of carbohydrate, 62 gm. of protein, and 125 gm. of fat. No insulin was required. The patient was last heard from September 16, 1936, when he reported his condition as being unaltered though generally good.

A diagnosis of thrombo-angiitis obliterans was made by one of us (Horton) as well as by the late Dr. George E. Brown and by Allen Adson. The degree of calcification in the arteries around the right ankle was so slight that, had we not been critical, we would have called the roentgenograms negative. The diagnosis of thrombo-angiitis obliterans may be open to criticism, but we feel that the occlusive process in the left leg as well as in the ulnar arteries is much more likely to have been this than arteriosclerosis obliterans. The fact that the condition improved when the patient stopped smoking would tend to substantiate this fact. The diabetes was of very mild type, as indicated by a moderate reaction to the glucose tolerance test. The patient's condition was very well compensated for, and he had been taking excellent care of himself.

*Case 2.* The second patient was of German descent and was 45 years of age when admitted to the clinic on July 16, 1936. Claudication pain had developed in

his left leg for the first time in December 1934, and tingling and burning pain and tenderness in the left toes were noticed in March 1935. A fairly severe superficial and deep "phlebitis" of the entire left leg suddenly developed in May, 1936. This condition gradually cleared up, but there remained slight residual dependent swelling. Cigarette consumption had averaged 20 to 40 per day for 30 years. Lack of nail growth on the left foot had been noticed for one year. There was no history of ulceration.

When elevated, the left foot exhibited blanching, grade 3 plus, and when lowered, rubor, graded 2 plus, with fairly rapid return of color to the toes and distal half of the foot. The patient had noticed these changes in color since the onset of the condition. The left calf muscles were tender, grade 3, and the nails of the left foot were atrophic and irregular. The popliteal, posterior tibial and dorsalis pedis arteries on both sides were occluded. The radial, ulnar and femoral arteries were open. Laboratory tests gave negative results except for showing the presence of 14 gm. (3.87 per cent) of sugar in the urine, a value for blood sugar of 270 mg. per 100 c.c. on admission, and slight calcification of the arteries of the left thigh. Fifty units of insulin were sufficient to render the urine free of sugar and a diet of 111 gm. of carbohydrate, 65 gm. of protein, and 142 gm. of fat maintained it so. Circulation in the left foot improved to a marked degree following the intravenous administration of typhoid vaccine and the use of the Sanders bed and the Pavaex machine.

On August 31, 1936, a rather severe pain suddenly developed in the right foot. Ten days later the patient reentered the clinic with evidence of marked circulatory insufficiency in this foot. Elevation of this right foot produced pallor, grade 4, in 30 seconds; rubor, graded 2 to 3, developed in one and three-fourths minutes when the foot was in a dependent position. It was evident that the collateral circulation of the right foot had suddenly become partially occluded. The popliteal, dorsalis pedis, and posterior tibial arteries had previously been occluded. Blanching was absent, but there was prompt return of rubor, grade 2 plus, when the left foot was dependent. Examination of the urine gave negative results but the value for blood sugar was 176 mg. per 100 c.c. The same type of diet was administered as before. Repeated intravenous injections of typhoid vaccine were again given and this, together with Pavaex therapy, resulted in rapid improvement in the circulation of the right foot.

The patient entered the clinic for the third time on June 26, 1937, having three months or so previously sustained a traumatic abrasion over the left lateral malleolus. A large ulcer, measuring 6 by 6 mm., had formed there and this was present at the time of the patient's admission. On elevation there was pallor, grade 1, of both feet, with rubor, grade 1, on dependency. Arterial pulsations were the same as at the time of the previous admissions except that pulsations in the right ulnar artery were now graded 2. The diabetes was under adequate control, the value for blood sugar being 160 mg. per 100 c.c. No sugar was detectable in the urine. By the use of typhoid vaccine, Pavaex therapy, and postural exercises the ulcer rapidly healed.

The presence of phlebitis, the occlusion of the arteries of the lower extremities, and partial occlusion of the ulnar arteries, associated with symptoms of intermittent claudication and the excessive use of tobacco, leave little doubt as to this being a case of thrombo-angiitis obliterans, especially since the patient was previously healthy. The sudden onset of pain in the leg which even until a short time after the patient's first admission had not in any way troubled him, despite the lack of pulsations, further corroborated the diagnosis. The diabetes mellitus was mild and readily controlled by diet; the part it played in the course of the obliterating process can remain



only one of conjecture. The slight calcification of the arteries of the left thigh does not militate against the diagnosis of thrombo-angiitis obliterans.

Pavaex therapy was employed in this case in conjunction with typhoid vaccine and the patient was afforded much relief. It is unusual in our experience to see a patient derive so much benefit as did this one from the use of the Pavaex apparatus, though the use of typhoid vaccine was the more effective on the patient's third visit.

*Case 3.* This patient, a Russian Jew, 44 years of age, registered at the clinic on October 26, 1936, with a history of intermittent claudication in the right calf and arch of the foot after walking three blocks. This was first noted in the fall of 1930. An ulcer, which healed slowly, appeared on the right fifth toe at the same time. In April, 1936, a gangrenous, discharging and very painful ulcer had developed on the right third toe at the edge of the nail. This toe had been amputated in August but the stump had not healed. Pavaex and other therapy had been of no avail. The patient smoked 10 cigarettes daily. No symptoms were noted referable to the left leg.

On examination at the clinic pulsations were found to be absent in the right dorsalis pedis and posterior tibial arteries; pulsations were normal in all other arteries. On elevation, there was pallor, grade 2, of the right and of grade 1, of the left foot, whereas on dependency, the right foot exhibited rubor, grade 3, in the second to fourth toes and metatarsal region. Rubor was not observed in the left foot. There was no history of phlebitis. Roentgenograms of the legs were negative.

The diabetes was of a fairly severe grade; value for the blood sugar was 345 mg. per 100 c.c. on admission and sugar in the urine was graded 4. Control of the diabetes, however, was fairly easily effected by the use of 75 units of protamine insulin and 10 units of old insulin, together with a diet consisting of 143 gm. of carbohydrate, 69 gm. of protein, and 158 gm. of fat. All other laboratory tests gave essentially negative results.

The circulatory disturbance in the feet improved following the intravenous injection of typhoid vaccine. It was necessary to amputate the second right toe; healing occurred promptly. The patient was last heard from on October 31, 1937, at which time he said he was confined to bed because of his foot.

This patient was only 39 years of age at the time intermittent claudication developed in the right calf and arch. The subsequent course in this case makes the diagnosis of thrombo-angiitis obliterans reasonably certain.

*Case 4.* This man, a Jew, aged 40 years, registered at the clinic August 14, 1934, with symptoms of intermittent claudication and numbness in both thighs, calves, and left arm, the limit he was able to walk being one or two blocks. These symptoms had been present since the sudden onset of sharp pain in the right fifth toe in October, 1933. Three weeks later, color changes of the three phase type, developed. In another five months a black spot appeared on the dorsum of the right fifth toe but disappeared after intensive heat treatment for four weeks. Since February 1934, the patient had noted postural changes in color in his feet and, in March of the same year, had injured his right leg, healing having taken place in eight weeks. There was no history of phlebitis, but the patient's feet were cold most of the time.

Since the age of 14 up to February 1934, the patient had smoked one package of cigarettes daily but since had limited his consumption to six or less cigarettes daily. He had known about his diabetes since 1931, and it had been adequately controlled by diet. In October 1933, the value for blood sugar was 135 mg. per 100 c.c. and the urine was free of sugar. On admission, the value for blood sugar was 112 mg. per

100 c.c.; the glucose tolerance test showed a rise to 211 mg. at the end of the second hour, with a drop to 118 mg. at the end of the third hour, each corresponding specimen of urine containing 3.23 per cent, or 1.66 gm., of sugar. A routine specimen of urine gave a negative test for sugar.

On examination at the clinic, there was found to be blanching, grade 3, of the feet on elevation, with rubor, grade 3, on dependency, greater on the right than on the left. Normal pulsations were present in all of the arteries except the popliteal, posterior tibial, and dorsalis pedis arteries which were occluded. A roentgenogram of the right lower leg was negative but one of the thorax showed calcification and torsion of the arch of the aorta.

The diagnosis in this case of thrombo-angiitis obliterans is probably correct. The patient's diabetes was of a mild type. Treatment consisted of postural exercises, Pavaex therapy, contrast baths, and injections of padutin. The diabetes was controlled by a qualitative diet, but there was no improvement in the patient's condition, at least not up to September 14, 1936.

*Case 5.* This patient, a real estate dealer of French-Spanish descent and 56 years of age, was first admitted to the clinic on April 10, 1935. He had three ulcers on the right leg and foot. These ulcers had developed following sudden arterial occlusion in March 1934. The patient had been a very heavy smoker for many years and had noticed a sense of fatigue in both calves on walking, ever since an attack of typhoid fever in 1915. Actual claudication pain first developed two years prior to this admission, the limit he was able to walk being two or three blocks.

While the ulcers had at first resisted all forms of treatment, even right femoral periarterial sympathectomy which had been performed elsewhere, they finally healed after seven months' treatment at the clinic; this treatment consisted chiefly of applications of saline and Dakin's solution, pinch grafts, and *aloë vera* leaf. The brachial and radial arteries were found to be fully open; the ulnar, femoral, popliteal, posterior tibial, and dorsalis pedis arteries were occluded. The right foot showed rubor, grade 2, and the left, grade 0 to 1, on dependency, with pallor, grade 2 plus, of both feet on elevation. Slight calcification of the arteries of the right leg was revealed by a roentgenogram. The patient had a history of diabetes but no evidence of this could be found.

The patient returned to the clinic on April 1, 1937, an ulcer having spontaneously developed on the lower portion of the left leg four months previously. Claudication pain had persisted, now coming on after walking one block. The ulcer finally healed in a little over two months following the continued application of warm saline and boric acid packs, alternating every two hours, with nocturnal applications of cod liver oil. At this time, the arterial pulsations were the same as previously. A roentgenogram of the left leg was negative. Examination of the ocular fundi gave practically negative results, no sclerosis of the vessels being noted. The diabetes was now more severe, being of grade 1; the value for blood sugar was 138 mg. per 100 c.c. and there was an occasional trace of sugar in the urine. The diet consisted of 140 gm. of carbohydrate, 63 gm. of protein and 114 gm. of fat; 10 units of protamine insulinate were prescribed.

While it is somewhat difficult to classify this case from the standpoint of the occlusive arterial disease, because of occlusion of the ulnar arteries as well as those of the lower extremities and the practical absence of evidence of arteriosclerosis, we are inclined to regard it as one of thrombo-angiitis obliterans. Even so, however, we are still at a loss to explain the occurrence of the ulcers on the legs and the extreme slowness of healing.

## SUMMARY

Five cases of thrombo-angiitis obliterans associated with diabetes mellitus have been reported which were seen at the clinic since the latter part of 1932. Prior to this, five similar cases had been seen here, Adams having reported one in 1930 and one of us (Horton) and Allan, four in 1934, the interval histories of which are briefly recorded. Three of the patients whose cases are reported in this paper were 47, 44, and 40 years of age and of Jewish descent, whereas one was 45 and of German descent and the other 56 and of French-Spanish descent. The diagnosis of thrombo-angiitis seems fairly well established in these cases.

The part diabetes mellitus plays in the course of the arterial obliterating disease is not definitely understood, but the indications are that if not adequately controlled it may tend to hasten it.

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## SOME LIMITATIONS IN PREVENTIVE MEDICINE \*

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SINCE death from old age is inevitable, and since death of the aged in all probability will continue to result most frequently, as at present, from processes of deterioration and degeneration of body organs and tissues, what limitations on preventive medicine should be expected, and how will all of this influence the work of doctors? This is the problem I have set myself for discussion. Let me make it clear at the outset that I write not as one expert in preventive medicine but as one, who has spent his life time chiefly in teaching medicine and directing a medical service in a hospital, in these capacities watching disease in patients, trends in the science and art of medicine and reactions of students, undergraduate and graduate, and their teachers to changing aspects of medicine since I began its study nearly 42 years ago. Furthermore, what I write is intended to be in no way a criticism of the accomplishments of preventive medicine. That they have been truly great I gladly acknowledge.

In a broad sense preventive medicine means the science and art of preventing the occurrence and development of disease; usually the term is limited so as to be used in reference to human beings; however, prevention of disease in animals may be a necessary factor in the prevention of disease in human beings, and to this extent disease in animals needs to be included in any study of preventive medicine. Diseases in man can be divided into those that are preventable and those that are not preventable; we may have methods of decreasing incidence of some of the latter and yet can not prevent them; strictly speaking they are not preventable diseases. Curability or satisfactory methods of treatment are not regarded as an integral part of prevention, although they may be important contributory factors of prevention.

It is difficult to estimate with any degree of accuracy the proportion of preventable diseases that at present are seen by practitioners; apart from the contagious diseases of childhood that are preventable and syphilis, they do not make up any very large proportion of general practice, even if to these is added tuberculosis, not strictly a preventable disease but yet one influenced in frequency by the methods of preventive medicine. In a general hospital medical service of adults preventable disease causes very few admissions. Into such wards come surprisingly few patients that can be used for illustration in courses of preventive medicine.

Possibly some idea of the relative importance in medicine of preventable diseases can be gained by the proportion of descriptive text in a textbook of medicine that is devoted to preventable and non-preventable disease. Interpreting preventable disease very liberally, in a recent edition of Osler's

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"Principles and Practice of Medicine" of some 1100 pages of text, 300 pages are used in the description of preventable disease and 800 pages for describing diseases which enter very little or not at all into a consideration of preventive medicine. This may not be a good index of importance. At least, however, it suggests that the student is expected to devote more than two and a half times as much application to learning about non-preventable as about preventable disease.

Those diseases that play a major part in bringing about the demise of the old in general belong to the group of non-preventable diseases, and preventive medicine, certainly at present, exerts no direct effective influence on them or at most but a slight and indirect one to delay somewhat their onset. Preventive medicine, however, does have an effect on the soil in which the degenerative diseases thrive. As preventive medicine prevents, there will be less of preventable disease and more of non-preventable disease; the list of preventable disease should lengthen. If preventable disease more and more is prevented, there will be a decreasing mortality from preventable disease. Such a change has been operative now for many years, and it appears to be effective with an increasing efficiency.

Perhaps the most notable effect of preventive medicine has been the increase in life expectancy at birth; in 1800 life expectancy is supposed to have been between 25 and 35 years; in 1815 it was calculated to be 38.7 years; in 1900 each new born infant had a life expectancy of a little less than 50 years; now the life expectancy at birth has passed 60 years; 61.2 years in 1933. If mortality by age groups is analyzed, it will be found that this life expectancy increase has come almost entirely as the result of preventive medicine effective on the young. In other words, preventable disease occurs chiefly in the young, and its prevention saves life, in the main, of the young. This is shown particularly clearly by the following figures: in 1901 one-quarter of the population died in the first 24 years of life, while in 1933 this time had been lengthened to 52 years; in 1901 half the population died in 58 years of life, while in 1933 this period had been lengthened to 68 years; the gain had dropped from 28 years to 10 years; much more striking is the greatly lessened difference, 4 years, between the age at which three-quarters of the population died in 1901, 74 years, and in 1933, 78 years, a gain of only four years. Preventive medicine in other words, as it succeeds, is increasing the number of older people in our population, and this will have a profound influence on the economic as well as the medical situation. To put it another way, preventive medicine seems destined to decrease the importance of pediatrics and to increase the importance of geriatrics; the younger are becoming healthier, while the older increase in relative numbers only to suffer, perhaps to suffer more frequently and relatively earlier, the diseases incident to, in fact unavoidable in, the older decades of life. Curiously enough statistics indicate that, while older people grow more numerous, the really old do not increase but even seem to decrease. "Life span" appears not to have increased. All of this would

suggest that preventive medicine keeps many young people from dying in their youth to become sub-par risks in their older years, that our preventive medicine keeps many from dying but fails to endow them with what might be regarded as a greater normal expectancy of health in their old age, possibly actually a decreased expectancy.

From the preceding it seems reasonable to deduce that preventive medicine by success in accomplishment will increase the need of the population for medical attention. If mortality in youth is decreased by preventive medicine, as seems to be happening, sickness, and particularly serious sickness, in the young will decrease, and the physician will have less work in treatment and more in prevention, so far as individual preventive methods are concerned. Preventive medicine, however, brings its results more largely from betterment of general hygiene and methods of living in which the individual physician plays no great personal part and from which he can benefit in fees but little. The statement has been made that increased application of preventive medicine would decrease the physician's earning power. However, with more people becoming older, and old people not living any longer than before, as the results of betterment of methods of preventive medicine more individuals may be expected to develop degenerative disease and the younger ones of this group seemingly to become increasingly susceptible to, and possibly live longer with, degenerative diseases. The result of this will be that physicians will have more and more work to do, chiefly in taking care of degenerative disease in the old, i.e. in practicing geriatrics.

This change is shown, too, in an interesting way by the shift in relative importance of the chief causes of death from period to period. In 1900 the 20 conditions causing the largest number of deaths in the United States were in order of their frequency as is shown in table 1. If we contrast the order of frequency for 1935 as shown in table 1, the shift downward in importance of preventable diseases and upward of non-preventable diseases is a strikingly notable feature. Tuberculosis is seen to have fallen from first place in 1900 to sixth place in 1935, pneumonia from second to third (not much change), diarrhea and enteritis from third to thirteenth, congenital malformations and diseases of early infancy from fifth to eighth, diphtheria from tenth to twenty-third, typhoid and paratyphoid from eleventh to twenty-fifth, cirrhosis of the liver from thirteenth to eighteenth, measles from fourteenth to twenty-fourth, whooping cough from sixteenth to twenty-first and malaria from twentieth to twenty-second. Broadly speaking these are preventable diseases. In contrast heart disease has shifted in the opposite direction from fourth place in 1900 to first in 1935, nephritis from sixth to fourth, cerebral hemorrhage and softening from eighth to fifth, cancer from ninth to second, suicide from seventeenth to twelfth, appendicitis from eighteenth to fourteenth and diabetes from nineteenth to tenth; of these all are non-preventable on the basis of present knowledge except possibly suicide. Accidents, which are preventable, have not been pre-

TABLE I  
Chief Causes of Death

1900	1935
1. <i>Tuberculosis (all forms)</i>	1. Heart disease
2. <i>Pneumonia (all forms)</i>	2. Cancer and other malignant tumors
3. <i>Diarrhea and enteritis</i>	3. <i>Pneumonia (all forms)</i>
4. Heart disease	4. Nephritis
5. <i>Congenital malformations and diseases of early infancy</i>	5. Cerebral hemorrhage and softening
6. Nephritis	6. <i>Tuberculosis (all forms)</i>
7. External causes	7. External causes
8. Cerebral hemorrhage and softening	8. <i>Congenital malformations and diseases of early infancy</i>
9. Cancer and other malignant tumors	9. Automobile accidents
10. <i>Diphtheria</i>	10. Diabetes mellitus
11. <i>Typhoid and paratyphoid</i>	11. Influenza
12. Influenza	12. Suicide
13. <i>Cirrhosis of liver</i>	13. <i>Diarrhea and enteritis</i>
14. <i>Measles</i>	14. Appendicitis
15. Hernia and intestinal obstruction	15. Hernia and intestinal obstruction
16. <i>Whooping cough</i>	16. Syphilis
17. Suicide	17. Homicide
18. Appendicitis	18. <i>Cirrhosis of liver</i>
19. Diabetes mellitus	19. Other puerperal causes
20. <i>Malaria</i>	20. Puerperal septicemia
21.	21. <i>Whooping cough</i>
22.	22. <i>Malaria</i>
23. Syphilis	23. <i>Diphtheria</i>
24.	24. <i>Measles</i>
25.	25. <i>Typhoid and paratyphoid</i>

Bold face type: Diseases causing an increasing percentage of mortality rate

Italics: Diseases causing diminishing percentage of mortality rate

vented and with the advent of the automobile have been increased markedly. Influenza, of the infectious diseases, is the only one that has not changed its place essentially in the five year periods from 1900 to 1935 (table 2); as a result of the great epidemic, it shifted from eleventh and twelfth places in 1935 and 1900 respectively to eighth in 1920 and for some reason fell to fourteenth place in 1910. It is interesting that influenza, which in the 1918-19 period caused probably the worst epidemic ever known to man, shows no significant shift in rating as a cause of death in this period in which preventive medicine has been so thoroughly studied and its methods so extensively applied. Influenza, so far, has resisted all methods of control; were there now another great pandemic of influenza, it is doubtful whether we are in any better condition to cope with it than in 1918-19. Those of us, who were confronted in 1918-19 with medical and preventive treatment of influenza, realized our almost complete helplessness then, and we know that today we could do little better than we did 20 years ago.

Another way of getting an idea of present limitations of preventive medicine is to discuss a few typical non-preventable diseases. Let us consider some of the diseases that are grouped as non-preventable or but little preventable. Take as an example Bright's disease, nephritis. So far as we know its causes, Bright's disease is due to an inflammatory process or

TABLE II

Principal causes of death. Rates for 1935, and relative position in 1935 compared with relative position in 5-year periods, 1900 to 1930, inclusive according to reports of the Bureau of the Census. Expanding registration area in Continental United States

Cause of Death	1935		Relative Position						
	Rate per 100,000	Relative Position	1930	1925	1920	1915	1910	1905	1900
Diseases of the heart.....	213.1	1	1	1	1	1	2	2	4
Cancer and other malignant tumors.....	107.9	2	2	4	6	6	8	9	9
Pneumonia (all forms).....	81.8	3	4	3	2	3	3	3	2
Nephritis.....	81.2	4	3	2	4	4	5	5	6
Cerebral hemorrhage and softening	76.6	5	5	6	7	7	9	8	8
Tuberculosis (all forms).....	55.0	6	6	5	3	2	1	1	1
External causes (a).....	50.1	7	8	8	9	9	7	7	7
Congenital malformations and diseases of early infancy.....	49.4	8	7	7	5	5	6	6	5
Automobile accidents (b).....	26.8	9	10	11	17	23	25	—	—
Diabetes mellitus.....	22.2	10	12	12	11	10	13	16	19
Influenza.....	22.1	11	11	10	8	12	14	12	12
Suicide.....	14.3	12	13	14	18	11	12	13	17
Diarrhea and enteritis.....	14.1	13	9	9	10	8	4	4	3
Appendicitis.....	12.7	14	14	13	13	15	18	17	18
Hernia, intestinal obstructions....	10.3	15	15	15	16	17	16	15	15
Syphilis.....	9.1	16	17	18	19	19	22	23	23
Homicide.....	8.3	17	16	17	23	21	23	22	24
Cirrhosis of the liver.....	7.9	18	19	21	22	14	15	14	13
Other puerperal causes.....	5.8	18	18	16	14	18	20	19	21
Puerperal septicemia.....	4.1	20	23	23	24	22	21	21	22
Whooping cough.....	3.7	21	22	22	15	20	19	18	16
Malaria.....	3.5	22	25	25	25	25	24	25	20
Diphtheria.....	3.1	23	20	20	12	13	11	11	10
Measles.....	3.1	24	24	24	20	24	17	20	14
Typhoid and paratyphoid fevers..	2.8	25	21	19	21	16	10	10	11

(a) Excludes deaths from automobile accidents, and automobile-railroad-street car collisions.

(b) Excludes deaths from automobile-railroad-street car collisions.

to a degenerative vascular disease, the latter predominating. Today there is no known effective preventive of degenerative vascular disease, and so in this group preventive medicine has no place. As to the other group, those due to an inflammatory process, the great majority of cases today follow upper respiratory tract infection or pyelitis. To date nothing seems to have succeeded in preventing or even reducing the incidence of the common cold which starts the great majority of upper respiratory tract infections. With pyelitis we can do much to ameliorate symptoms, but except for those associated with some form of obstruction of renal outflow we rarely cure. It would seem that pyelitis is an increasing factor in the production of chronic Bright's disease. Even when we recognize Bright's disease at its very onset, we have little to advise either for cure or for prevention of ultimate progress into the chronic stage that will kill; progress



probably can be slowed, but that is all. Preventive medicine is very limited in its effect on Bright's disease; yet Bright's disease ranks fourth among causes of death.

Similarly with chronic cardiac disease preventive medicine has relatively little to offer. In earlier life, up to about 40, rheumatic fever is the cause of most cases of chronic heart disease, and we have almost nothing to offer by way of prevention. Past 40 chronic non-valvular disease increasingly dominates the picture, often in association with or as a sequence to hypertension; here preventive medicine offers nothing in any wise effective. In later adult life there is a considerable but not large incidence of chronic heart disease from syphilis of the aorta and a slight incidence from syphilis of the coronaries or myocardium. Although so far preventive medicine has not shown any very striking effects in this last group, still control of syphilis is becoming increasingly effective, and with this in due season, 10 to 15 years after syphilis control becomes effective, we will see marked reduction in the group of chronic heart disease caused by syphilis. Thus preventive medicine so far offers little in the case of chronic heart disease which now ranks first in the lists of causes of death. However, there is some brightness in the future in this group as concerns syphilitic heart disease, which makes up a not large percentage of chronic heart disease mortality and is preventable when we apply measures already understood.

Cerebral hemorrhage in very large measure results from degenerative vascular disease except in cases of syphilitic origin; here as to prevention we are well nigh helpless. Cerebral vascular disease is credited with fifth place in death causes. Apart from syphilitic brain disease, chronic brain disease including the psychoses can be influenced only slightly by preventive medicine.

Tuberculosis is a disease in which over a long period of years there has been a steadily decreasing mortality. From the slant of the curve in relation to specific methods of prevention the steady fall suggests the influence of general conditions such as betterment of home conditions rather than the results of planned methods of preventive medicine, though the latter must have had influence. In a sense this may seem a discouraging situation as regards preventive medicine. Actually it really is the opposite, indicating how the application of general betterment of living, improved hygiene, etc. may accomplish much even when there are practically no direct methods of prevention available.

Such communicable diseases of childhood as measles and whooping cough show, in standardized curves of mortality, improvement from general measures only, extremely similar to that seen in scarlet fever, in which disease some specific preventive methods have been used. These three mortality rates in 1935 reached essentially the same level as that of diphtheria, a disease in which we have a good method of determining susceptibility, a method of protection and a specific serum for therapy. The difference is that whereas in 1911 the death rate per 100,000 between the ages of 1 and

14 of measles was approximately 32, scarlet fever 35 and whooping cough 22, that of diphtheria was about 78. In 1936 at all ages the rate per 100,000 was, for measles approximately 0.9, scarlet fever 1.9, whooping cough 2 and diphtheria 2.4.

In cancer and other malignant tumors of course, as yet, we have no effective preventive measures and can not expect to have in the present state of our knowledge. The only encouraging feature about these is that, using curves of mortality standardized in relation to the number of people living at each age period, these malignant tumors are not increasingly causes of death in the United States. All available evidence seems to show that cancer and other malignant tumors are not increasing in actual incidence beyond the fact that, as more people live into the age of their maximal occurrence, more people will develop them until such time as some means of prevention is discovered.

Pneumonia remains, as yet, a non-preventable disease; its incidence seems to be very unchanging from decade to decade in all parts of the country. So far newer methods of treatment have not been effective enough or applicable generally enough to cause any apparent real decrease in mortality from pneumonia. That is a very curious and disquieting situation not only with regard to pneumonia but also with regard to other diseases in which great improvement in methods of treatment have been developed in the past decade. In the very illuminating and extremely interesting study of the Metropolitan Life Insurance Company, recently issued, which has this title "Twenty-Five Years of Health Progress" only two diseases seem to be increasing definitely as causes of death among their 17,000,000 insured individuals; these are diabetes mellitus and appendicitis of whose effective therapy we know so much. Why this is so I have no explanation to offer; statisticians seem satisfied that it is a fact.

Finally there is another fact that must be thought about in connection with preventive medicine. The occurrence of numerous infectious diseases, especially the contagious diseases of childhood, creates a resistance, which possibly continues into the next generation. Certainly mild attacks prevent subsequent and possibly more severe attacks. Communities, not so protected, suffer increased incidence and severity with increased mortality, when these infectious diseases do appear. In the great War soldiers from urban centers were more resistant than those from country districts to measles, for example, in which the mortality became very high. Records show that the introduction of one of these contagious diseases into countries, in which they had not occurred previously, would cause very great mortality. This suggests that, if preventive medicine completely conquers these diseases, and they disappear as a result, a great danger of their reappearance in epidemic form with high mortality might be expected. This is a possible danger of prevention by isolation as contrasted to prevention by increasing resistance. It raises the thought, too, that if a given disease, say diphtheria, is eradicated by protective measures, such as the use of toxin-antitoxin or toxoid,

will it be possible, when the disease no longer is occurring, to persuade people to continue these protective measures, or will they become careless and soon an unprotected generation grow up to become the soil for spread of a malignant type of the disease? Past experience with vaccination against small-pox makes this seem definitely a possibility. Perhaps complete success in prevention is undesirable for those diseases, in which a very considerable resistance under present conditions of occurrence is present. Certainly many of man's experiments, intended or unintended, have upset biological balances. The introduction into the United States of such pests as the English sparrow, the starling, the chestnut blight, the boll weevil, the elm tree disease, etc., suggests this possibility. Perhaps, after all, a very complete success of preventive medicine may not be a complete blessing.

### SUMMARY

As preventive medicine succeeds, non-preventable disease increases in relative importance. Preventive medicine by increasing life expectancy has increased the number of older people, but, as there appear to be no greater number of very old people, "life span" has not been increased. This suggests that preventive medicine by its success has resulted in there being more sub-par, older people subject to the degenerative diseases that are non-preventable. These changes in quality and proportion of population in various age groups are increasing the importance of geriatrics at the expense of pediatrics. These trends would seem destined to increase the need for practitioners; the greater demand for their ministrations will be to make more comfortable the progress of non-preventable disease, which will be very largely the degenerative diseases of older age. Practically complete elimination by methods of preventive medicine of the communicable or contagious diseases may, if it occurs, create the soil for extensive epidemics of these diseases with a high mortality, and in this sense not be desirable. Whatever the developments of preventive medicine, it seems probable that certain, apparently inevitable, limitations will persist, and as the result of these, the need for physicians will increase rather than decrease; only they will deal more and more with older patients and less and less with younger ones.

# CASE REPORTS

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## THE SO-CALLED SUPERIOR PULMONARY SULCUS TUMOR\*

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THE term "superior pulmonary sulcus tumor" was introduced by Pancoast<sup>1</sup> in 1932 to designate a special tumor producing a complex that was characterized by: (a) Pain around the shoulder and down the arm; (b) Horner's syndrome (unilateral ptosis, miosis, enophthalmos and anhidrosis); (c) roentgen-ray evidence of a small homogeneous shadow at the extreme apex, of local rib destruction, and often of infiltration into the adjacent vertebrae; (d) atrophy of muscles of arm and hand; (e) and finding a tumor at the thoracic inlet. Pancoast based his conclusions on a study of seven cases. Four of them he had reported already in 1924.<sup>2</sup> In none of the cases was a necropsy performed, and in only two of them were biopsies performed. One of these biopsies was diagnosed as *carcinoma spinocellulare*, the other was diagnosed by the examining pathologist as a carcinoma. However, Pancoast disregarded that diagnosis because he could not detect a primary growth and concluded the growth was a distinct entity which might have its origin in an embryonal epithelial rest, possibly from the fifth pharyngeal pouch. In two of the cases there was a history of carcinoma of the cervix four and two years prior to the presenting illness. The possibility that in these two cases the apical tumors were late metastatic growths was disregarded. Pancoast also stated, "One can practically rule out primary lung carcinoma. Certainly it does not produce Horner's syndrome as an early manifestation."

Pancoast justified the new term by stating that it implies the approximate location of the tumor and a lack of origin from the lung, pleura, ribs, or mediastinum.

The sulcus is a groove situated posteriorly in the thorax and running longitudinally along each side of the vertebral column. The tumor is situated at the upper pole of this groove and at the posterior aspect of the thoracic inlet at the level of the second, third, and fourth thoracic vertebrae. The lesion is placed in the region of the common trunk, from the eighth cervical and first thoracic, at least.

Pain usually starts under the lateral border of the scapula. This is due apparently to the involvement of the origin of the posterior division of the first and possibly the second thoracic common trunks. Later the pain radiates high in the axilla and this is due to the involvement of the branch of the first thoracic. The upper arm pain corresponds to the supply of the intercosto-humeral, from the second thoracic. Pain in the ulnar aspect of the forearm suggests the sup-

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ply of the internal cutaneous from the eighth cervical and first and second thoracic nerves. Rarely, instead of the pain in the areas mentioned, numbness and weakness are present.<sup>1</sup>

Pancoast was apparently aware of the fact that his concept of this superior pulmonary sulcus tumor as being of a specific type was based on inadequate evidence, because he stated, "It is possible that this new designation may be changed again with a better knowledge of the histopathology of the growth." That statement is interesting in view of the fact that Pancoast was apparently little impressed by the remarks of Evans, the discussor of his first paper of 1924.<sup>3</sup> Evans stated, "I feel convinced that it is not possible to make a positive diagnosis in tumors of the upper thorax without microscopic aid, and further that any type of growth in this part of the thorax will produce symptoms similar to those described by Pancoast in his case." In his own five cases with the same clinical picture a different type of tumor was found in each: (1) carcinoma metastatic of the breast (eight years after removal), (2) sarcoma of the thymus, (3) carcinoma of the apex of the lung, (4) sarcoma of the apex of the lung, (5) sarcoma developing underneath the scapula. Evans concluded his remarks by saying: "I do not think it possible to differentiate these tumors by clinical or x-ray findings alone."

A cursory review of the literature reveals that a symptomatology identical with the one described by Pancoast has been recorded many times. Browder and De Veer<sup>4</sup> quote a report of Hare<sup>5</sup> who saw a case of rapidly growing tumor in the inferior triangular space of the left side of the neck. The initial complaint had been pain in the shoulder and along the course of the ulnar nerve of the left arm with tingling and numbness over this area. Some months later there had developed contraction of the left pupil and the levator palpebrae ceased to perform "its office." The patient died about four months after the onset of symptoms. At autopsy, a hard nodular tumor mass was found to involve the large arteries and veins of the left side of the neck, extending upward as far as the origin of the brachial plexus. The phrenic and pneumogastric nerves and the sympathetic with its lowest cervical ganglion were surrounded by tumor tissue and transformed into the diseased structures. The tumor extended also under the clavicle, surrounding the subclavian artery and vein and destroying most of the anterior scalene muscle. The case was considered an instance of "glandular scirrhus."

Ricaldoni<sup>6</sup> described in 1918 a carcinoma of the upper lobe of the lung that was confirmed by a necropsy. It had all the clinical findings of the so-called superior pulmonary sulcus tumor. Ricaldoni concluded that it is necessary to form a separate group of "infiltrating lesions of the pleural dome."

It was recognized early that the symptomatology was due to damage to the lower part of the brachial plexus and to the cervical sympathetic. The damage may be due to tumors of various origins; to an inflammatory process, for example tuberculosis; to a cervical rib; or to trauma.

Courcoux and Lereboullet<sup>7</sup> stated in 1931, "The disturbances which cause the compression of the cervical sympathetic by a lesion of the pleural dome are at present classic."

Da Rin<sup>8</sup> called attention to the possible occurrence of exophthalmos and mydriasis instead of enophthalmos and miosis particularly early in the disease, due to irritation of the sympathetic before it becomes paralyzed. Proptosis was

actually observed in a case reported by Dutt Gupta,<sup>9</sup> who found at necropsy a bronchiogenic carcinoma.

In his monograph on primary carcinoma of the lung, Fried<sup>10</sup> states, "This phenomenon seen occasionally in bronchiogenic cancer is due to paralysis of the sympathetic nerve involved by either the new growth or an early malignant or inflammatory apical pleuritis."

Tobias<sup>11</sup> reported five cases with the characteristic symptomatology. Four of them were due to carcinoma of the lung and the fifth to a metastatic carcinoma of the stomach. In two of his cases with carcinoma of the lung the diagnosis was confirmed by necropsy. The paper of Tobias has the descriptive title: "Síndrome Apico-costovertebral doloroso por tumor apical; Su valor diagnóstico en el cáncer primitivo pulmonar."

Pardal, Ferrari, and Itoiz<sup>12</sup> reported coexistent tuberculosis and primary apical carcinoma with the symptomatology of the "superior pulmonary sulcus" tumor.

Jacox<sup>13</sup> reported a case, with necropsy, of a mucin producing adenocarcinoma of the right pulmonary apex. He concluded that the superior pulmonary sulcus tumor is an atypical form of a primary bronchiogenic carcinoma.

Steiner and Francis<sup>14</sup> reported two cases of bronchiogenic carcinoma at this site. One of them was confirmed by necropsy, the other by biopsy.

Additional case reports with the characteristic symptomatology and with necropsy findings were reported by Fried,<sup>15,17</sup> Browder and DeVeer,<sup>4</sup> and Connolly.<sup>16</sup>

Fried recorded the characteristic clinical and roentgen-ray findings in two cases with the necropsy findings of a squamous cell carcinoma in the region of the left sternoclavicular articulation invading the supra and infraclavicular fossae, the clavicle and the three upper ribs. The pleura, lungs, and the other viscera were not involved. Fried considers that the tumor originated from epithelial rests of the lower bronchial clefts.

The case report of Frost and Wolpaw<sup>18</sup> is particularly interesting because they found at necropsy a mediastinal tumor extending into the right pleural cavity, and invading the apex of the right lung. The histological findings were those of a sympathoblastoma originating probably from the inferior cervical sympathetic ganglion. The clinical and the roentgen-ray findings were those of a superior pulmonary sulcus tumor.

The report of Marzil and Crawford<sup>20</sup> dealt with a 47 year old man with the characteristic pain but without the syndrome of Horner. The necropsy revealed an adenocarcinoma of the pulmonary apex infiltrating and destroying portions of the first, second, and third ribs and the adjacent vertebrae. This case is instructive because it demonstrates the destruction of ribs and vertebrae without the presence of Horner's syndrome.

Kelman and Schlezinger<sup>21</sup> described a case with the characteristic clinical features and with the necropsy findings of a tumor near the apex of the left lung, which extensively invaded the neck, compressed the cervical cord and metastasized to the sacral spinal cord. The tumor did not originate from the lung; a branchial origin was considered but did not appear very likely. The exact pathologic nature and origin of the neoplasm was not determined.

To the case reports dealing with the clinical picture of the superior pulmonary sulcus tumor we wish to add a case of a typical "superior pulmonary

sulcus tumor," diagnosed during life and confirmed by necropsy, which showed it to be a primary adenocarcinoma of the right upper lobe bronchus.

### CASE REPORT

C. M., white, aged 31, single, American, taxicab driver, entered the Mount Sinai Hospital on the service of Dr. I. M. Trace, March 9, 1936, complaining chiefly of pains in the right shoulder and chest, loss of weight, weakness, and cough, of three months' duration.

*Onset:* He was in good health until about three months previous to admission, when he began experiencing pain in the right scapular region. This was not related to effort or change of weather. Soon the pain spread to the top of the shoulder, right axilla, and right infraclavicular area. The nature of the pain was like that of a sharp stab being more marked at night. It had become progressively worse in the last month, and, as a result, he was entirely incapacitated. The pain was not referred to the fingers, and movement of body did not bring on this pain. The usual methods of treatment by his physician gave no relief. Cough appeared soon, following the pain. At first, it was slightly blood streaked, and moderately productive. It disappeared about four weeks prior to entrance. He had lost about eight pounds in weight, and he was becoming progressively weaker. He perspired at night, but not enough to require changing his night shirt. His appetite was poor, and he slept very little because of his pain. His previous history was of no importance. He had had gonorrhea five years previously. He was supposed to have had diabetes for which he had not been treated.

*Physical Examination:* A fairly well nourished man of 31, comfortably sitting in bed, not dyspneic or cyanotic. His temperature was 99° F., pulse 86 and regular, blood pressure 120 systolic and 70 diastolic. The eyes presented no abnormalities. Pupils were not abnormal. The tonsils were ragged and cryptic. The teeth were in poor condition. The thyroid was diffusely enlarged, soft, and smooth. There were no abnormal pulsations in the neck nor were glands felt. There were a few prominent venules in the right supraclavicular fossa. The heart measured 9 cm. to the left and 3.5 cm. to the right of the midsternal line. The first sound was somewhat roughened.

The lungs presented moderately impaired resonance over the right apex posteriorly, the supraclavicular fossa, and down to the second right intercostal space, anteriorly. The breath sounds were somewhat roughened posteriorly, but subdued over the supraclavicular fossa and anteriorly in the infraclavicular area. No râles were heard. The mediastinum was seemingly not disturbed.

The right shoulder and arm did not present any abnormalities. The patient presented no limitation of motion. He could rotate, adduct, abduct, and raise his right upper extremity without bringing on any discomfort. The color and temperature of this extremity seemed to be normal. There was definite tenderness on pressure over a rib at the inferior angle of the scapula, as well as on pressure in the second and third interspace, and over the second rib at the midclavicular line.

The abdomen, genitalia, and lower extremities presented no abnormalities. The reflexes were normal and rectal examination revealed no abnormalities. No glands were palpable in the groin, axilla, or epitrochlear regions. Neurological examination revealed no objective findings to explain this localized pain.

*Laboratory Findings:* The urine contained a trace of albumin and a few pus cells. The blood examination showed hemoglobin 80 per cent (Sahli), red blood cells 4,300,000, and white blood cells 12,460. There were 76 per cent neutrophils, 20 per cent small lymphocytes, 2 per cent eosinophiles, and 2 per cent plasma cells. The blood chemistry revealed sugar 82 mg. per 100 c.c. of blood, urea nitrogen 12 mg., and calcium 9 mg. The Wassermann and Kahn tests were negative. The

sputum was negative for tubercle bacilli on many occasions. The basal metabolic rate was minus 5 per cent. The sedimentation test was slightly above normal.

*Roentgen examination:* The chest film revealed the right apical region slightly narrowed and superimposed by a homogeneous cloudiness reaching downwards as far as the first anterior rib end, going over without any sharp borderline into the normally aerated tissue. There was in addition obliteration of both costophrenic angles. Roentgen diagnosis of an old thickened apical pleura was made. (Figure 1.)

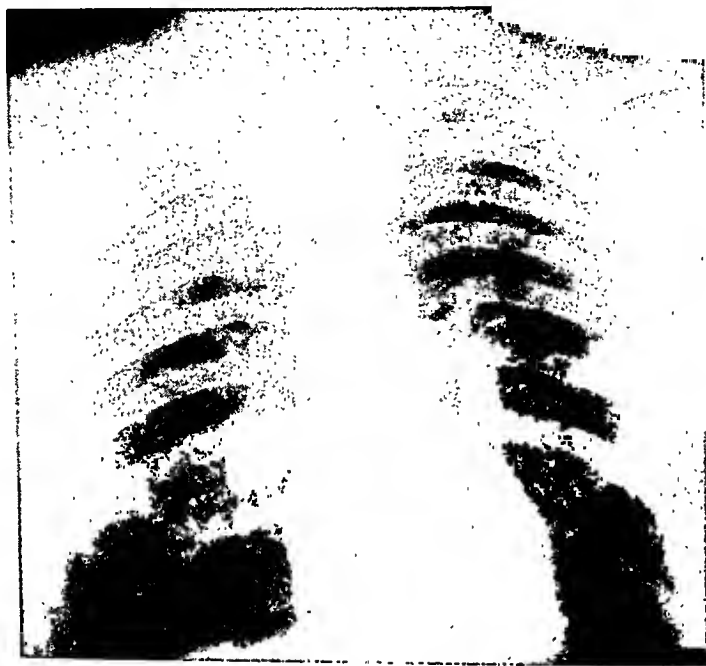


FIG. 1. (2/25/36) Chestfilm reveals a cloudiness occupying the cupula of the right lung with no sharp limitation downwards.

*Clinical Impression:* Because of the severe and intractable pain, which required morphine, and the apical shadow on the chest film, one of us (L. F.) entertained the possibility of a "superior pulmonary sulcus" tumor in this case. With this in view, another roentgen study, especially for bone visualization was requested. The film showed that the bony structures at the right thoracic inlet revealed normal calcium content and regular outline of the upper ribs, transverse processes, and lower cervical and upper thoracic vertebrae. (Figure 2.) A bronchoscopy and bronchography by Dr. J. Lifschutz showed a good filling of the upper bronchus up to its fine ramifications, thus ruling out a bronchial carcinoma originating from a larger ramus.

The patient was discharged after a two weeks' stay without a definite diagnosis. He was observed in the outpatient department by one of us (L. F.) On May 23, 1936, about 10 weeks following the first examination, early manifestations of Horner's syndrome were noticed. There was slight narrowing of the right palpebral fissure and absence of sweating on that side of the face. The pupil was not abnormal. Roentgen examination on this date showed that in addition to the apical shadow seen previously, the paravertebral portion of the second rib showed at its lower aspect a definite interruption of its contour which presented a ragged appearance. The right arch of the second thoracic vertebra was destroyed. (Figure 3.) The diagnosis of superior pulmonary sulcus tumor became more evident. Roentgen-ray therapy was instituted.



The patient was readmitted to the hospital for one week's stay. He was found to have lost some more weight and strength. He had a leukocyte count of 20,600 and 82 per cent were polymorphonuclears. Pneumothorax (300 c.c. of air) was done with the view of possibly delineating the tumor. The films only showed broad adhesions of the pulmonary apex with the chest wall.

A month later, during one of his dispensary visits, we noticed that he had a fully developed Horner's syndrome. (Contracted pupil, enophthalmos, narrowed palpebral fissure, and absence of sweating on the side affected.) He complained of severe pain, and sneezing or jarring would aggravate it. All the muscles of the right shoulder girdle, arm, forearm and hand showed atrophy, and there was definite weak-



FIG. 2. (3/11/36) Perfectly normal appearance of the bony structures at the thoracic inlet. Roentgenologically the diagnosis of malignancy is not yet possible.

ness. There was also hyperesthesia of the inner aspect of the right arm. There was marked tenderness in the right axilla, over the clavicle and second interspace. No glands were felt in the supraclavicular fossa. There was venous distention over the right chest, arm, and neck. A positive diagnosis of superior pulmonary sulcus tumor was made.

The patient received deep roentgen-ray therapy from June 29 to July 16, 1936, under 0.73 copper plus 1.0 mm. aluminum; 12 treatments of six anterior and six posterior exposures. A total of 1,500 R. air given with 200 KV peak, 5 milliamperes, 50 cm. distance, going 10.5 R. minute. There was for a short period a decrease in pain, but paresthesia, weakness, and rapid progress were in no way influenced by the treatment.

The patient's final admission to the hospital was on September 26, 1936. He was extremely emaciated and in great agony. He needed morphine every hour. All the findings mentioned above were more outstanding. There was more distention of the veins over the right chest and shoulder. There was extreme atrophy of the muscles of the shoulder, arm, forearm, and hand. The slightest movement gave him excruciating pain.

Roentgen film showed marked bone destruction from the first to the third thoracic vertebra. The vertebral arches of the first, second, and third vertebrae had

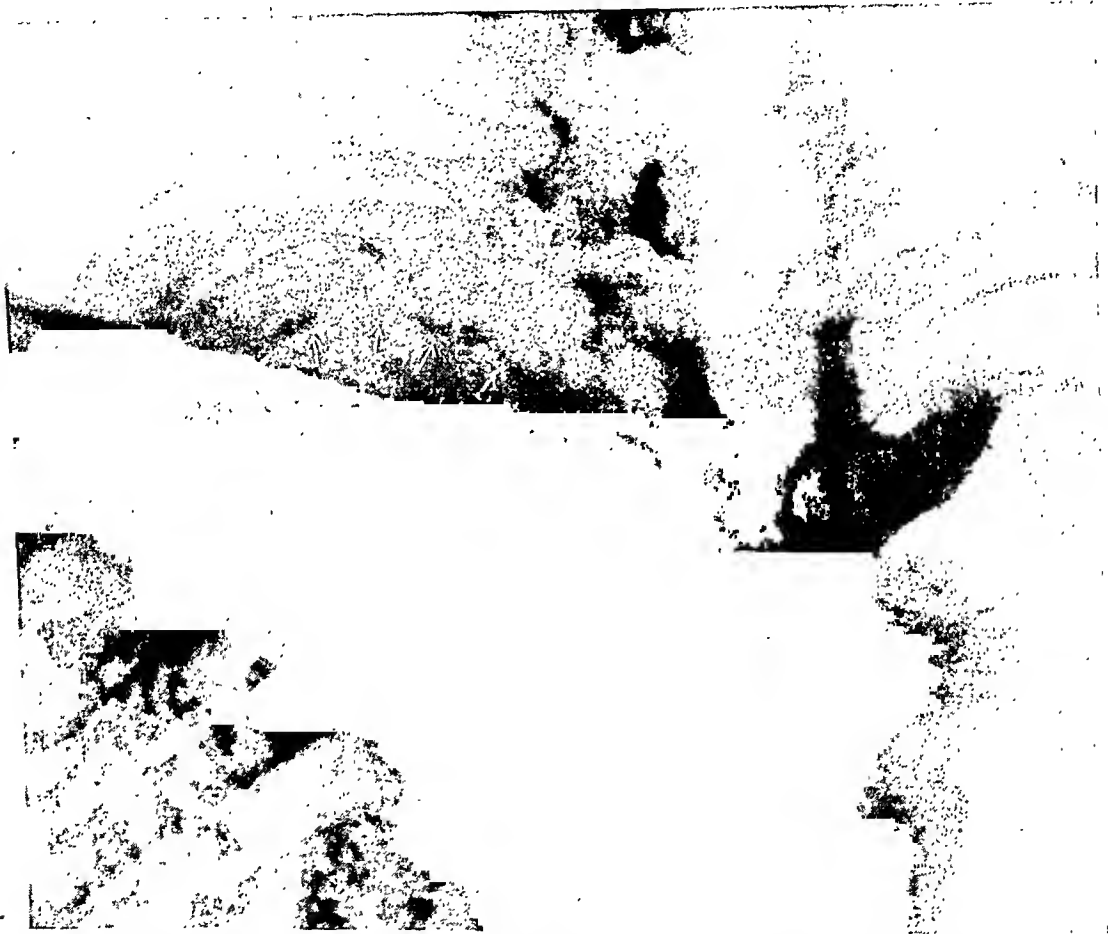


FIG. 3. (5/29/36) The paravertebral portion of the second rib, the transverse process and the arch of the second vertebra show ragged outlines and bony defects. Definite signs of malignancy.

disappeared. There were defects in the first three ribs, besides changes of the transverse processes. (Figure 4.)

The urine contained 0.4 per cent sugar on one occasion but his blood sugar was not abnormal. He developed a bronchopneumonia in the left lung and died on October 8, 1936, about two months after the onset of symptoms.

§ *Differential Diagnosis:* Tuberculosis with apical pleuritis was considered first. The slight rise in temperature, the early cough, the roentgen findings of an apical shadow and the pain were in favor of such a diagnosis on his first admission. However, the severity of the pain was much more marked than that experienced in tuberculous apicitis. Later, of course, the bone changes ruled it out entirely.

Primary malignant growths of the ribs and vertebrae do not, as a rule, cause such a syndrome. Besides, roentgen evidence is apt to be present earlier than in this case.

Spinal cord tumor and tumor of the mediastinum were considered and ruled out because of lack of neurologic findings and roentgen evidences.

*Necropsy:* The necropsy was performed one hour after death.

The essential findings follow: The body was extremely emaciated. Flat bulges were present over the proximal portions of the first three right ribs. The supra- and infra-clavicular fossae were deeply retracted on the right side and distinctly less on

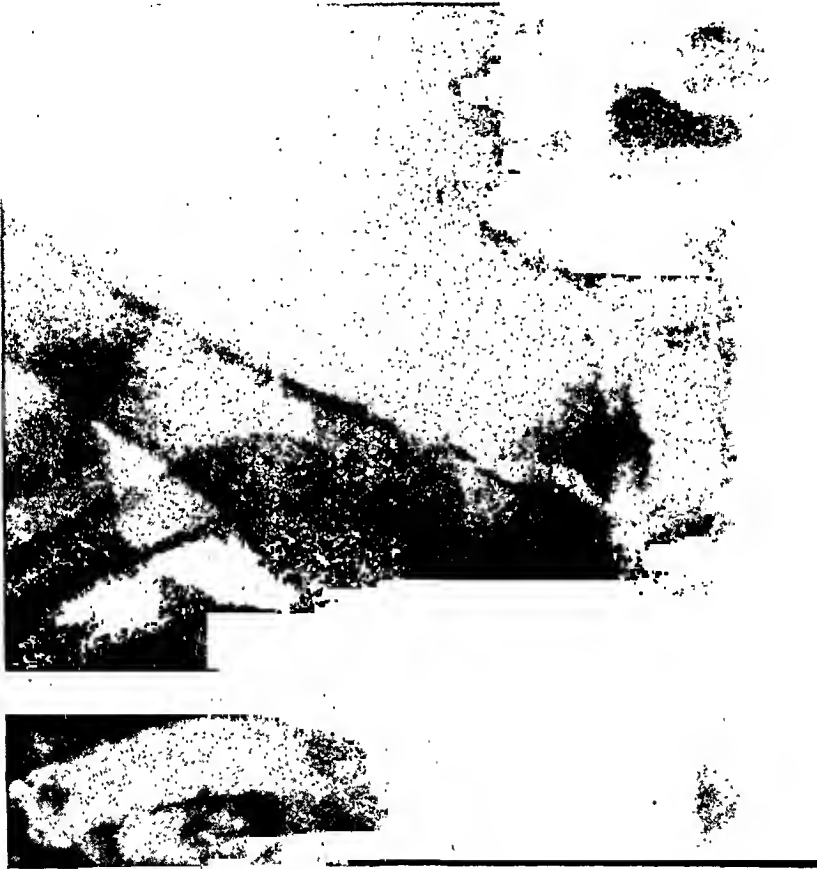


FIG. 4. (9/28/36) The upper three ribs, second and third transverse processes, vertebral arches and half of the second vertebral body are destroyed on the right side.

the left. The right arm was thinner than the left due to wasting of muscles. A few firm lymph nodes measuring about 10 mm. in size were felt in both axillary fossae, none elsewhere. The right half of the diaphragm was elevated (at the level of the fourth rib; the left half was at the level of the fifth interspace). The right pleural cavity was obliterated by adhesions which increased in density towards the apex. The lower and middle lobes of the right lung contained less air than normally; the upper lobe was completely atelectatic. The upper lobe was infiltrated with grayish-white firm tissue. Section surface: The borderlines between the infiltrating tissue and the pulmonary parenchyma could not be everywhere clearly recognized. Gray atelectatic tissue surrounded firm homogeneous infiltrating tumor parenchyma in which were enclosed compressed bronchi and blood vessels. The infiltration extended into

the pleura and through it into the dorsal portions of the first, second and third ribs. Over the outer surface of these ribs, flat bulges of a soft tissue were present which, when incised, showed yellowish soft semiliquid contents. The nerve trunks of the brachial plexus, as well as the right subclavian artery and its branches, were seen to traverse tumor tissue.

Vertebral column: Medially the tumor tissue extended and invaded the bodies of the first, second, third, and fourth thoracic vertebrae and their right transverse processes. The body of the second vertebra was partly, and that of the third vertebra was completely destroyed. Just a few small remnants of bone were present. The tumor tissue surrounded the vertebrae and invaded the adjacent soft tissues, but everywhere remained extradural. The spinal cord in this area was free.

Trachea: The mucosa was pale. About 3 cm. above the bifurcation it was imbedded in tumor tissue on the right side. The hilum lymph nodes on the right side were enlarged and in places matted together. The uppermost measured 3 by 1 by 1 cm. Its upper half was infiltrated with tumor tissue. The lower end showed an old calcified tuberculous lesion. A similar tuberculous process was present in the enlarged and anthracotic right peribronchial lymph nodes. The right main bronchus was filled with a reddish viscid exudate. The lower branch of the right bronchus was free. The upper and middle branches of the right bronchus were narrowed by the external pressure, but the mucous membrane was intact as far as the branches could be followed up. The upper bronchus entered the firm tumor tissue.

The left lung weighed 515 gm. and was somewhat enlarged. The pleura showed dense, fibrous adhesions. The apex showed some chronic emphysema. The mid-portion of the upper lobe was consolidated in an area measuring 11 by 8.5 cm. The bronchi were filled with a viscid exudate. The mucous membrane was congested and showed numerous hemorrhagic extravasations in the upper bronchus. The other bronchi were pale. On section surface of the consolidation, a sharply circumscribed area was present separated by a grayish line of demarcation and showing breakdown and necrosis in the center. It was brown red in color. The remaining parenchyma showed moderate emphysema. The lymph nodes showed no abnormalities.

The pancreas weighed 66 gm. It was decreased in all dimensions. The consistency was very firm. It was surrounded by infiltrated lymph nodes. On section surface the head of the pancreas was infiltrated by tumor tissue. The body and tail showed less marked changes. A cystic cavity, filled with a hemorrhagic fluid was present, measuring about 8 mm. in size, in the body of the organ.

The right suprarenal weighed 15.6 gm. and appeared larger than normal, measuring 60 by 40 by 15 mm. Section surface showed a replacement of the normal structure by nodes, yellowish white in color with multiple hemorrhages. The left suprarenal was larger than normal but not as large as the right, weighing 9.4 gm. Section surface showed also some infiltration.

The retroperitoneal lymph nodes were enlarged and matted together, measuring up to about 2 cm. The section surface was grayish white, obviously infiltrated and firm.

The left kidney weighed 145 gm. The capsule stripped with ease, except for a few isolated areas. The surface showed sharply circumscribed grayish white nodes which had a similar appearance on section surface. They varied in size from 10 to 15 mm. Their appearance on section surface resembled the tumor tissue described in the lung. Yellow streaks were especially noticeable. The cortex was widened up to 10 mm. There were nodes in the cortex as well as in the pyramids. The right kidney weighed 135 gm. and appeared somewhat larger than the left. The nodules were somewhat more numerous and larger. The kidney pelvis showed no abnormalities.

A few 3 mm. sized calcified nodules were found in the spleen and liver resembling grossly calcified tubercles. The brain and meninges were edematous.

*Microscopic examination:* Right lung: Sections from the tumor mass showed alveoli, small and large, of various shapes, lined with medium to high columnar epithelial cells with large, in places vesicular, in others hyperchromatic nuclei with prominent nucleoli. Some of the alveoli were very large and were filled with folds and papillary outgrowths. The anaplasia of the lining epithelial cells was very pronounced. Some of them were extremely large, of giant cell proportions, with single huge or with multiple nuclei. Mitotic figures were numerous. (Figure 5.) Some of the alveoli were empty but most of them were filled with a mucoid material. (Figure 6.) In sections stained with Mayer's muci-carmin the material in the alveoli stained similarly to mucus. Droplets of similarly staining material were seen also in the central portions of the lining epithelial cells. Some alveoli were filled with continuous sheets of cells similar in appearance to those just described, but many more alveoli were filled with large polygonal, oval or round cells with small compact nuclei and with a pale, hardly noticeable, cytoplasm. These alveolar masses resembled somewhat squamous epithelium, but only on superficial examination. (Figure 7.) The septums between the alveoli were made up of a dense connective tissue infiltrated with lymphocytes and with columns or nests of tumor cells. The resemblance to pulmonary alveoli is very striking. (Figures 8 and 9.) It could be assumed that the epithelium of the bronchus carcinoma grew out of the bronchi and lined the inner surface of the alveoli. That tempting supposition is contradicted by the finding of identical structures in the metastases in the kidney and suprarenals as will be described. (Figure 10.) One cannot assume there the preëxistence of alveoli to be lined by the ingrowing tumor cells. Furthermore the septa between the cavities in the lung have an entirely different structure than do pulmonary alveolar septa. In some areas small bronchi are seen compressed by infiltrating tumor tissue. A few nodules were found consisting of a calcified capsule and filled with a cheesy blue staining amorphous material. They resemble calcified tubercles.

Left lung: Sections from the consolidated areas show diffuse infiltration of the alveoli with a thick leukocytic and fibrinous exudate, surrounding centrally located necrotic broken down tissue, where the alveolar outlines can be made out very indistinctly. Towards the pleura, there is present a large area consisting of cavities separated by thick septa lined with cuboidal epithelial cells. They are regular in size, shape, and appearance. (Figures 11 and 12.) Such changes in pulmonary alveoli are known to occur in the course of chronic inflammatory processes. Some authors attributed them to transformation or metaplasia of the lining cells of the alveoli. Other writers (and they seem to have the better of the argument) claim that these cuboidal lining cells are not transformed lining cells but the basal cells of the bronchial epithelium which grew out of the bronchi and into the alveoli. In one of the sections such continuity of the cuboidal lining could actually be observed. (Figure 13.)

Pancreas: A diffuse infiltration with carcinomatous tissue is present having the same cytological and structural features as the primary tumor in the lung. The pancreatic parenchyma is diminished in quantity and is replaced by a diffuse proliferation of a dense, fibrous connective tissue which is infiltrated with lymphocytes and plasma cells. The connective tissue surrounds small atrophic islands of parenchyma and surrounds and compresses pancreatic ducts. The islands of Langerhans and the remaining parenchyma are equally affected. It is probable that the fibrosis is due to the compression of the ducts with resulting atrophy. Such atrophy and fibrosis are known to occur as a result of occlusion of the pancreatic ducts. Sometimes that is aggravated by a rupture of a duct with resulting necrosis and subsequent organization. That would be the most probable explanation for the formation of the cyst filled with necrotic and hemorrhagic contents as described in the gross findings. The cyst was found lined with carcinomatous tissue. In some sections, ducts were found compressed and deformed by infiltrating cancerous tissue. The increase of connective tissue and fibrosis could not be very well explained as merely a result

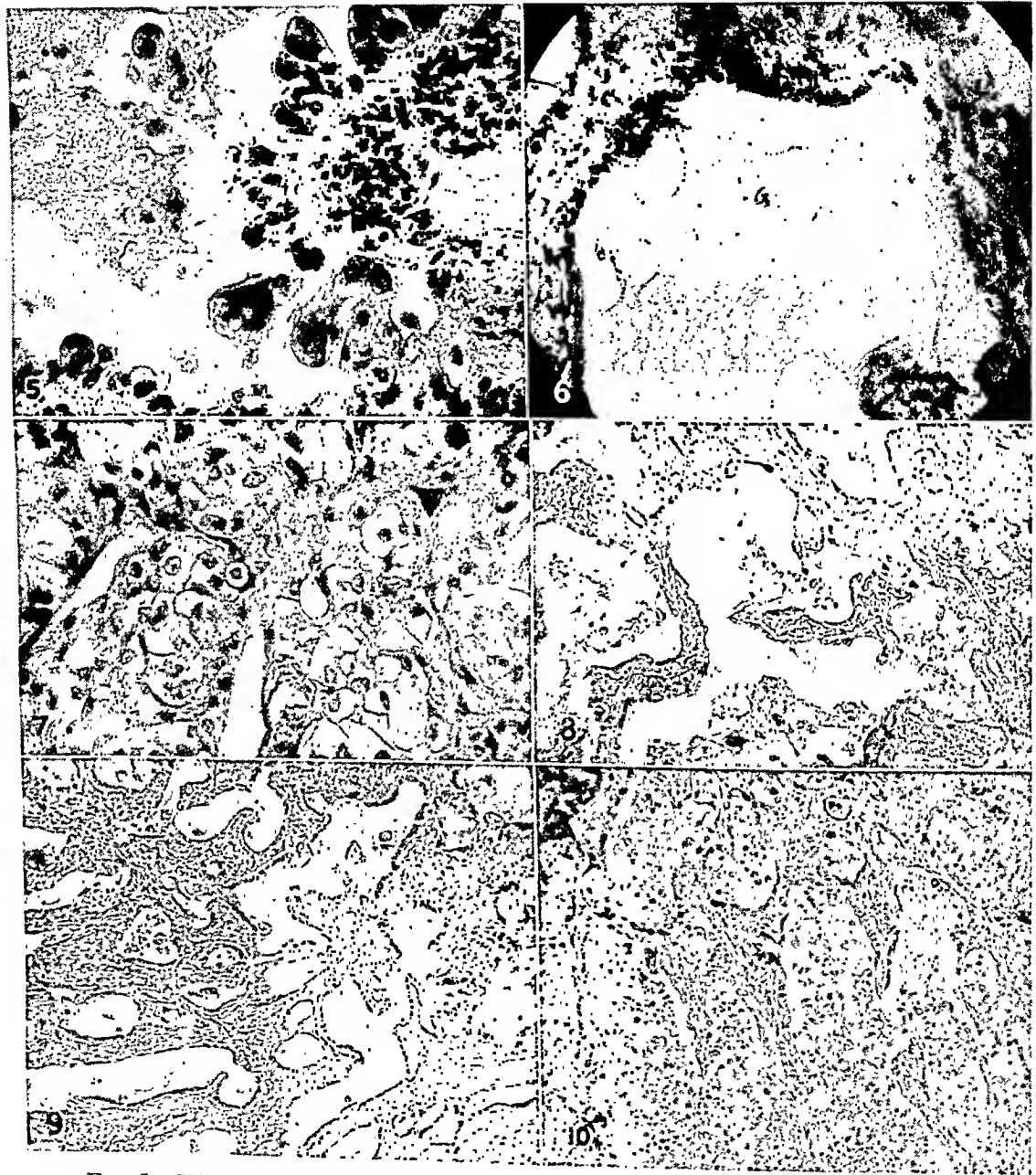


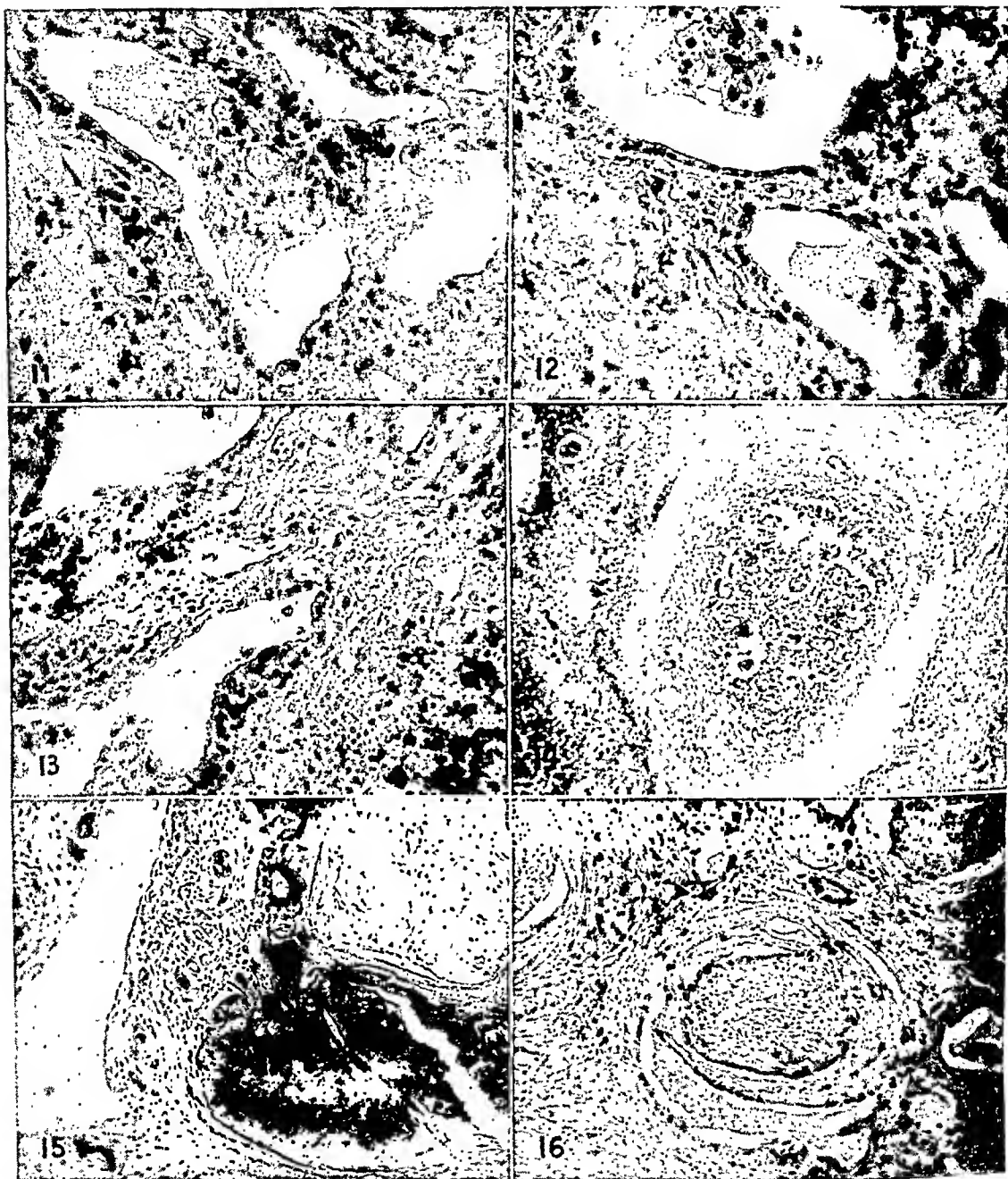
FIG. 5. High power magnification. The epithelial cells are very anaplastic. Many nucleated giant cells and mitotic figures are present.

FIG. 6. High power magnification. The alveoli are filled with a mucoid material staining with mucicarmum.

FIG. 7. High power magnification. The alveoli are filled with continuous masses of epithelial cells resembling squamous epithelium.

FIGS. 8 and 9. Low power magnification. Striking resemblance to pulmonary alveoli.

FIG. 10. Low power magnification. Section from a metastatic nodule in the suprarenal showing similar structure as in the tumor of the lung.



FIGS. 11 and 12. High power magnification. Cuboidal epithelial cells lining alveoli.

FIG. 13. High power magnification. Section through a small bronchus showing the continuity of the cuboidal epithelium in the alveoli with the basal epithelial cells of the bronchus.

FIG. 14. Low power magnification. Lumen of a blood vessel containing clumps of tumor cells.

FIG. 15. High power magnification. Destruction of bone by tumor tissue.

FIG. 16. High power magnification. Invasion of brachial plexus by tumor tissue.



of the cancerous infiltration, because it was equally pronounced in areas where cancerous infiltration was absent and only atrophic pancreatic parenchyma was present. Furthermore, an additional argument in favor of our explanation is the absence of any noticeable fibrosis in the metastases to the lymph nodes, kidneys, and suprarenals.

**Suprarenals:** Only small residues of the cortical layers are preserved. Most of the cortex and almost the entire medullary tissue is destroyed and replaced by a highly anaplastic adenocarcinoma similar to the tumor tissue that has been previously described. Its structure is identical with that of the tumor in the lung, including the resemblance to pulmonary alveoli. (Figure 11.) In some areas the tumor is sharply separated from the suprarenal proper while in others it grows diffusely into the parenchyma. The connective tissue is scarce.

**Kidneys:** The structure of the metastatic nodes is identical in every detail with that in the suprarenals. The renal parenchyma shows swelling of the tubular epithelium and a diffuse hyperemia.

**Lymph nodes:** (mediastinal, peribronchial, and retroperitoneal). The normal structure is hardly recognizable due to replacement by anaplastic actively proliferating tumor tissue of the already described morphology. Around some of the lymph nodes blood vessels were found filled with clumps of tumor cells. (Figure 14.)

**Vertebrae:** The bone is completely replaced by tumor tissue. (Figure 15.)

**Brachial plexus:** Sections showed nerve fibers surrounded by infiltrating carcinomatous masses. Mucoid degeneration and atrophy were noticeable (figure 16).

**Spleen and liver:** Sections of the nodules show the structure of old calcified tubercles.

**Anatomic diagnosis:** Primary adenocarcinoma of the right upper lobe bronchus infiltrating the chest wall, the right brachial plexus, infiltrating and destroying parts of the first, second, and third ribs, of the first, second, third and fourth thoracic vertebrae. Carcinomatous metastases to the mediastinal lymph nodes; to the tenth, eleventh, and twelfth thoracic vertebrae; to the retroperitoneal lymph nodes, to the pancreas, and to both suprarenals and kidneys. Atrophy of the right arm. Brown atrophy of the heart and liver. Cloudy swelling of the kidneys. Acute passive congestion of the spleen. Old tuberculous lesions of right mediastinal lymph nodes. Old calcified tubercles of spleen and liver.

## DISCUSSION

Primary apical bronchiogenic carcinomas are not very rare. The form which produces the symptom complex of the so-called superior pulmonary sulcus tumor is apparently quite rare. It occurred to us that the course and the pathological findings in this type of apical carcinomas may be explained by the presence of dense, pleural adhesions at the apex prior to the development and growth of the tumor. Such preëxisting adhesions may then facilitate the expansion of the tumor towards the thoracic wall and the spinal column. Many of the case reports emphasized the co-existence of old tuberculous lesions, such as we also found in our case, and these may explain the presence of old adhesions.

## CONCLUSION

This case report adds additional evidence that the clinical complex of pain in the shoulder and arm, Horner's syndrome, atrophy of the muscles of the arm and hand, roentgen-ray evidence of a mass at the extreme apex of the lung, and local destruction of ribs and of the adjacent vertebrae, is not due to a specific tumor, as was postulated by Pancoast, but may be caused by a variety of tumors of different origins. Our case and the review of the reports in the literature



that are corroborated by necropsy findings indicate that in most cases a primary bronchiogenic carcinoma has been the true nature of the neoplasm in the so-called superior pulmonary sulcus tumor. It is suggested that preëxisting pleural adhesions may have some bearing upon the direction in which the tumor grows.

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### PERNICIOUS ANEMIA UNASSOCIATED WITH ACHLORHYDRIA: CASE REPORT \*

By J. OWEN FINNEY, M.D., *Gadsden, Alabama*

BLOCH<sup>1</sup> was the first to report a case of pernicious anemia without achlorhydria. He assumed that the gastric secretion returned to normal in the period of remission. Prior to the use of modern diagnostic methods reports of instances of pernicious anemia in patients in whom free hydrochloric acid was demonstrated in the gastric contents were fairly numerous. Since the advent of present day hematologic technic and knowledge such observations have been less common. Oliver and Wilkinson<sup>2</sup> enumerate 74 cases obtained from a survey of the literature. Alsted<sup>3</sup> in a comprehensive study, including the report of Oliver and Wilkinson, was able to find only 32 examples that withstood critical analysis. To these he added two cases from his personal experience. The case reported by Harvey and Murphy<sup>4</sup> was not considered in Alsted's series but appears, in the opinion of the author, to be an undoubted case of pernicious anemia unassociated with achlorhydria. The rarity with which free hydrochloric acid is found in the gastric contents of patients with pernicious anemia justifies a report of the following instance.

#### CASE REPORT

P. S., a 60 year old white, married, male minister was first seen on June 6, 1938, complaining of "weakness and difficulty in walking." Approximately three years before admission he had first noted paresthesia of the feet and legs. This soon became associated with difficulty in walking, especially in the absence of light, and with a "loss of feet" while in bed. In the fall of 1935 he experienced a period of weakness, tired easily and was told by his friends that his skin was "yellow." The weakness and "jaundice" abated spontaneously after a few months. The difficulty in walking and the paresthesia improved but he had never been able to get about with his usual agility since the onset of the illness. He carried on the busy life incident to his calling in an acceptable fashion until four or five months before he presented himself for examination when weakness curbed his activity. For six weeks "jaundice" had been noted. Anorexia had been present for four weeks; to this he attributed a weight loss of 15 pounds (6.9 kg.). He had not been able to

\* Received for publication November 15, 1938.

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walk without the aid of a stick for two weeks and his feet felt as if there were "boards glued to the bottoms." For one week dyspnea on moderate exertion had been present. No vomiting or hematemesis had occurred. There had been a tendency to constipation for several weeks without abnormal stools having been observed. No relatives were known to have had periodic attacks of jaundice.

The patient's past history was irrelevant. He had always resided in the United States and always abstained from the use of alcohol and tobacco. One nephew had died from a teratoma of the testicle. No other familial diseases were known.

On examination the temperature was 99.2° F., the pulse 84 per minute and the respirations 18 per minute. The weight was 146 pounds (66.5 kg.) and the height 68 inches (170 cm.). The systolic blood pressure was 110 mm. Hg; the diastolic 70 mm. Hg. The patient was a well preserved, intelligent, coöperative, elderly white male who appeared to be chronically ill. The skin had a distinct lemon yellow tint; it was smooth, warm, moist, elastic and free from lesions. The hair was normal in distribution, texture and amount and was silvery white in color. The mucous membranes were generally pale to a striking degree but not otherwise notable. There was no local or general glandular enlargement. The head was symmetrical and without tenderness. The position of the eyes was normal; the extra ocular movements were well and equally executed; the pupils were equal, round, regular and reacted briskly to light but sluggishly in accommodation; the fundi were negative. The nose and ears were not remarkable. The mouth was edentulous. The tongue was not red nor was atrophy of the papillae noted. The neck was negative. The thorax was "barrel" shaped, symmetrical and well clad. The lungs were clear to percussion and on auscultation. There was evidence of mild emphysema. The apex impulse of the heart was not identified; there was no shock or thrill. Emphysema of the lungs rendered percussion of the cardiac outline unsatisfactory. The sounds were distant; the rate normal; the rhythm regular; there was a soft blowing systolic murmur over the apex that was not transmitted. The peripheral vessels were firm but could be compressed with ease. The skeleton revealed no tenderness or deformity. The abdomen was pendulous and soft; no viscera or masses were palpable; there was no tenderness. The genitalia were negative. Rectal examination revealed a normal sphincter tone; there was a rosette of external hemorrhoids; the prostate was symmetrically enlarged to a mild degree; no masses were felt. Examination of the extremities revealed pallor of the nail beds; arterial pulsations were normally present. Neurologic study revealed a symmetrical hypesthesia from the mid thighs down. There was an absence of vibratory sense over the bony prominences of the sacrum and lower extremities. The proprioceptive sense was markedly diminished in the lower extremities. He stood and walked with a wide base and the Romberg test was positive. The Babinski phenomenon was equivocal on both sides. No abnormality of the cranial nerves was detected. The sensorium was clear, memory excellent and speech normal. There was no demonstrable muscle weakness or atrophy. The abdominal and cremasteric reflexes were present and respectively equal. The deep reflexes of the upper extremities were present, active and respectively equal. The ankle jerks could not be obtained; the knee jerks gave an equally faint response on reënforcement.

*Laboratory:* There were 1,500,000 red blood cells per cu. mm. The white blood cells numbered 2,500 with the differential showing 58 per cent polymorphonuclear neutrophils, 2 per cent large lymphocytes; 38 per cent small lymphocytes and 1 per cent basophiles. The color index was 1.5. The volume index was 1.2. A stained smear revealed marked poikilocytosis and anisocytosis; the majority of the cells were large and well filled; polychromatophilic cells were seen with fair frequency and an occasional nucleated red blood cell was observed. The reticulocyte count was 0.5 per cent. The fragility test revealed normal resistance. The icteric index was 6 units. The van den Berg test was negative. The urine was clear, amber and acid

in reaction; there was a faint trace of albumin; sugar was absent; microscopic study of the centrifuged sediment revealed an occasional white blood cell and hyalin cast; bile was absent; urobilin was present. The gastric analysis revealed 37° free hydrochloric acid and 25° combined acid; there was no gross or occult blood. (The simple Ewald test meal was used without alcohol or histamine stimulation. This procedure was carried out on five different occasions and free hydrochloric acid varied from 18° to 37°.) The stool was firm in consistency and brown in color; there was no gross or occult blood; no ova or parasites were identified; there were no fatty acid crystals. The blood Wassermann reaction was negative. The spinal fluid was clear and under 6 mm. Hg pressure; there were 9 cells per cu. mm. in the undiluted fluid; sugar was present; there was a faint trace of globulin; the Wassermann reaction was negative; the colloidal gold curve and chloride content were not determined. The phenolsulphonephthalein renal function test revealed 85 per cent excretion in two hours. No liver function tests were done. The fasting blood sugar was 110 mg. per 100 c.c. The non-protein nitrogen was 28 mg. per 100 c.c.

Fluoroscopic examination of the chest, stomach and colon was reported to be negative.

*Impression:* 1. Macrocytic anemia (probable pernicious anemia without achlorhydria) with combined degeneration of the spinal cord. 2. Benign hypertrophy of the prostate gland. 3. Adentia.

*Course:* The patient was given 3.5 c.c. of liver extract\* intramuscularly once a day for three days, and then once each week for 10 weeks. Since this it has been given every two weeks. This relative frequency has been maintained with the hope of stimulating improvement in the cord symptoms. A general diet was employed. Two teaspoonfuls of brewer's yeast four times a day was prescribed.

The reticulocyte response was dramatic, a peak of 18 per cent having been reached on the eleventh day following institution of therapy (figure 1). The erythrocyte count and hemoglobin rose promptly; the color index was 1 at the end of the third week and has remained slightly less since (figure 1). The white blood cell count has varied between five and six thousand since the fourth week (figure 1). At the end of the first week of treatment anorexia ceased and a sense of well-being replaced the weakness that had been so pronounced on admission. The skin lost the lemon yellow tint after two weeks. The course was characterized by rapid general improvement. Progress of the neurological symptoms has been slow in contrast to the general response but after one month of therapy he was able to get about without the aid of a cane. After two months he volunteered the information that he no longer "lost his feet" at night and that he had participated in a series of revival services of several days' duration. He has continued to do well up to the time of this report.

### DISCUSSION

The absence of achlorhydria is no longer considered contradictory to the diagnosis of pernicious anemia.<sup>5, 6, 7, 8, 9</sup> It is well in instances where free hydrochloric acid is found in association with pernicious anemia to consider the thought of Morrison<sup>10</sup> who suggests that the oxyntic cells may both secrete the anti-anemic principle and excrete hydrochloric acid. Granting this possibility it appears reasonable to assume that in rare instances the two functions are not lost and although there is no longer a secretion of the anti-anemia factor the excretion of hydrochloric acid continues undisturbed.

The history of the presented case is entirely compatible with pernicious anemia. The physical examination was characteristic in all respects except for an absence of glossitis. Detailed laboratory study revealed the presence of free

\* Lilly's "Concentrated Liver Extract."

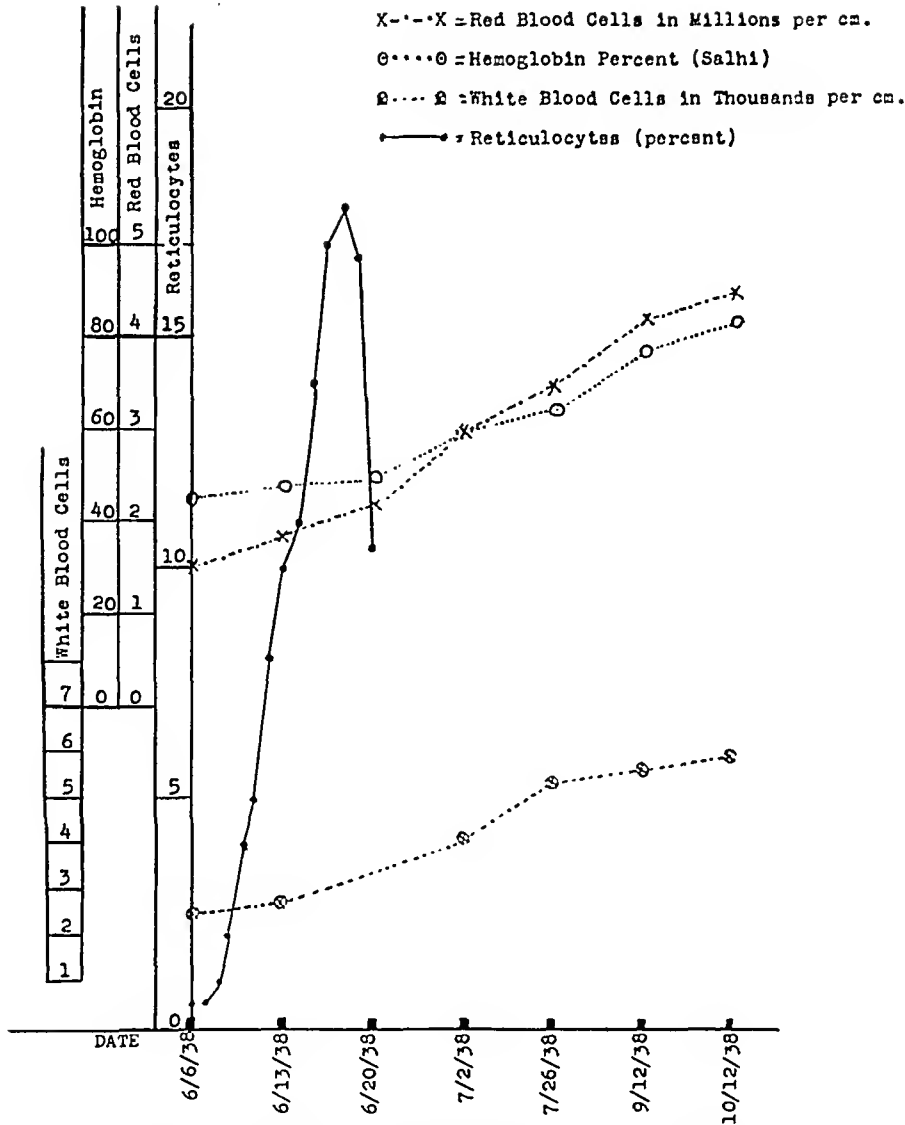


FIG. 1. Graphic demonstration of the patient's response to therapy. It will be noted that the red blood cell count and hemoglobin have been coordinated so as to indicate the color index. The color index was down to 1 at the end of the third week of treatment and has remained slightly less than 1 since.

hydrochloric acid in the gastric contents as the only unexpected finding. A gastrointestinal series failed to indicate any lesion. Care was exercised to see that the patient took a general diet during his convalescence, the so-called "sprue diet" being purposely avoided. Brewer's yeast by mouth and liver extract parenterally constituted the only therapy. The general and hematologic response was typical of pernicious anemia.

An interesting feature is that six weeks after the patient was admitted one of his relatives came into the clinic for study and was found to have pernicious anemia associated with glossitis and achlorhydria.

SUMMARY

A case is presented in which the history, physical examination and hematologic study were essentially characteristic of pernicious anemia. Free hy-

drochloric acid was found in the gastric contents in each of five different determinations. The response to parenteral liver extract was dramatic and in all respects similar to that in cases associated with achlorhydria.

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## PARTIAL HEART BLOCK DUE TO INCREASED VAGUS ACTION; A CASE REPORT\*

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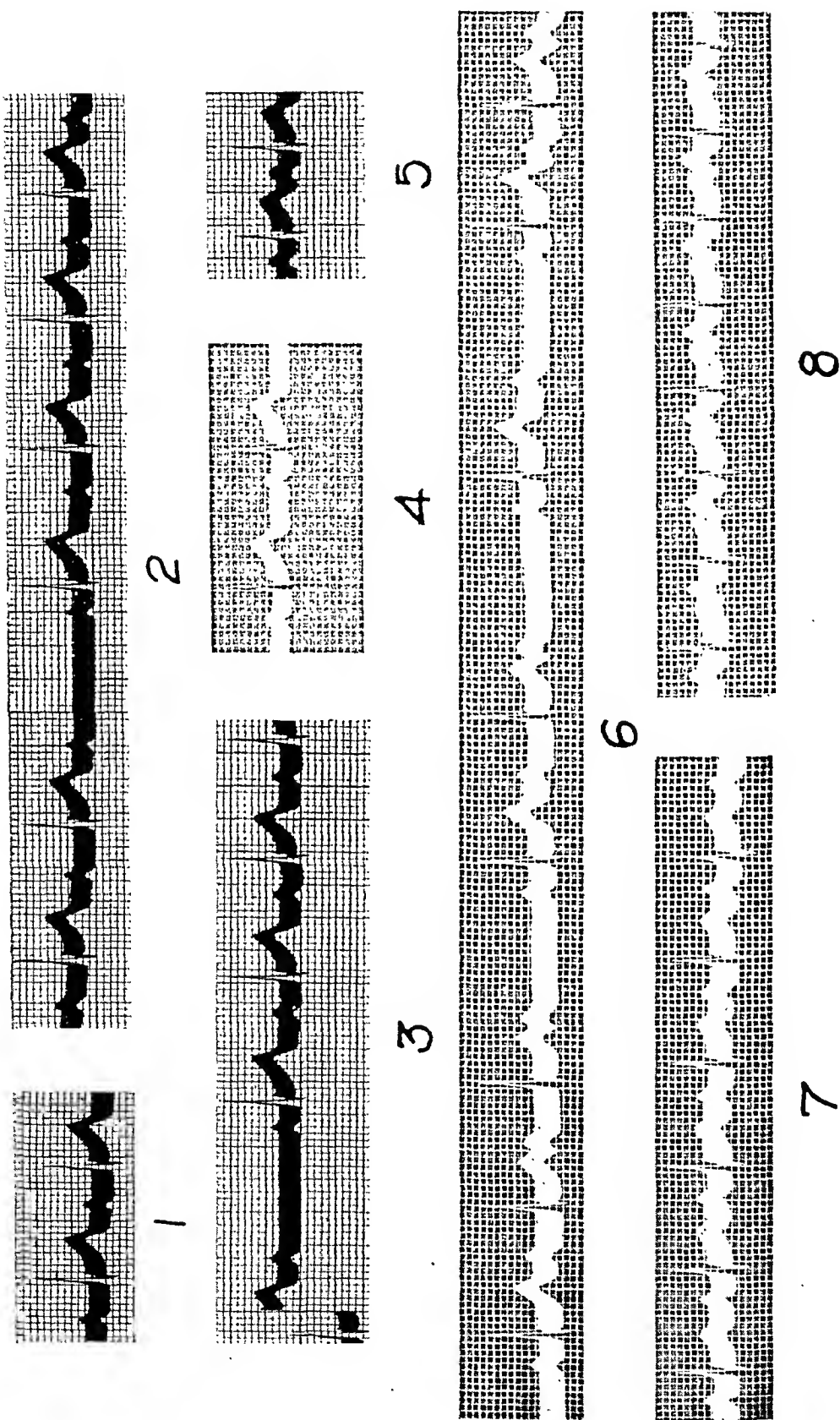
THIS rare case of severe heart block due to vagus influences is reported because of the paucity of such cases in the literature. It is felt that the report of such cases will help to draw attention to what must be of more frequent occurrence than the published instances would indicate.

## CASE REPORT

R. A., a 14 year old school boy, was referred to us in the Medical Clinic on December 30, 1933 to determine the cause of his fainting spells. He had been admitted to the Surgical Clinic on March 25 for a recent fracture of the right humerus, which was uneventfully set in a Dorfman's triangle. However, he had a fainting spell on four subsequent occasions, when he returned simply for the purpose of inspection. On these occasions he suddenly turned pale and lost consciousness for a minute but no convulsions occurred. After the fourth fainting spell, he was referred to us.

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Figs. 1-8.

He was a thin, undernourished boy with many carious teeth. His blood pressure was 104 mm. of mercury systolic and 74 diastolic and his heart rate was 68 per minute. Occasional intermittence of the pulse was noted, the pauses being  $1\frac{1}{2}$  to 2 times the ordinary pulse interval. This intermittence could be accentuated by holding the breath in inspiration and sometimes by pressure over the carotid sinuses. Exercise abolished the intermittence. A slight bulging was noted in the region of the pulmonary conus in the roentgen-ray, and this was confirmed by fluoroscopy. The electrocardiogram at this time showed a first and second degree A-V block with a P-R interval of 0.30 second and an occasional dropped ventricular beat. The patient showed no other clinical or laboratory abnormalities.

The past history revealed chicken pox, mumps and a questionable attack of scarlet fever in childhood.

The patient has been followed for a period of three years since his first visit without any change in the findings except for the occasional occurrence of a short, soft, blowing systolic murmur over the pulmonic area.

### SPECIAL OBSERVATIONS

During the succeeding three years, a number of special observations were made on this patient with the aid of the electrocardiograph, and the effect of various drugs was noted. The more pertinent observations are given in table 1 and shown in figures 1 to 8.

It was found that (1) holding the breath in inspiration increased the A-V block (see table 1 and compare figures 1 and 2); (2) pressure on the carotid sinuses sometimes increased the A-V block (see table 1 and compare figures 1 and 3); (3) exercise lessened the A-V block (compare figures 1 and 4); (4) digitalis (3.3 gm. in 9 days) increased the A-V block (see table 1 and compare figures 1 and 6); (5) atropine completely abolished the A-V block and prevented breath holding and carotid sinus pressure from affecting the A-V conduction (see table 1 and compare figures 1 and 5); (6) atropine abolished the A-V block present during digitalization (compare figures 6 and 7). However, adrenalin,

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FIG. 1. Portion of electrocardiogram, Lead II, taken March 3, 1934 showing first degree A-V block present in this patient. P-R interval 0.26 sec., rate 86.

FIG. 2. Portion of electrocardiogram, Lead II, taken March 3, 1934 showing increase in A-V block in this patient following holding of breath in inspiration. Note dropped ventricular beat and Wenckebach phenomenon. P-R interval 0.16 to 0.32 sec., rate 79.

FIG. 3. Portion of electrocardiogram, Lead II, taken March 3, 1934 showing increase in A-V block on this patient following pressure on right carotid sinus. Note dropped ventricular beat and Wenckebach phenomenon. P-R interval 0.16 to 0.24 sec., rate 80.

FIG. 4. Portion of electrocardiogram, Lead II, taken March 3, 1934 showing decrease in A-V block in this patient following exercise. P-R interval 0.18 sec., rate 86.

FIG. 5. Portion of electrocardiogram, Lead II, taken March 3, 1934 showing decrease in A-V block in this patient 15 minutes after administration of 1/50 gr. atropine sulphate hypodermically. P-R interval 0.18 sec., rate 111.

FIG. 6. Portion of electrocardiogram taken March 26, 1935\* showing increase in A-V block in this patient following administration of 2.3 gm. of digitalis over a period of 9 days. Note dropped ventricular beat and Wenckebach phenomenon. P-R interval 0.18 to 0.36 sec., rate 86 on average.

FIG. 7. Portion of electrocardiogram, Lead II, taken March 26, 1935\* showing decrease in A-V block in this patient 20 minutes after administration of 1/50 gr. atropine sulphate hypodermically. P-R interval 0.19 sec., rate 103.

FIG. 8. Portion of electrocardiogram, Lead II, taken March 26, 1935\* showing lack of action of breath holding and carotid sinus pressure in this patient 15 minutes after administration of 1/50 gr. atropine sulphate hypodermically. P-R interval 0.19 sec., rate 125.

\* These three records were taken after the patient had been completely digitalized.



TABLE I  
Studies Made on March 3, 1934

Procedure	Heart rate (beats per min.)	P-R Interval (sec.)	Remarks
Control . . . . .	86	0.26	No dropped ventricular beats (figure 1)
Breath held in inspiration . . . .	79 (average)	0.26 (0.16-0.32)	Dropped ventricular beats with Wenckebach phenomenon (fig- ure 2)
Pressure on right carotid sinus . .	80 (average)	0.22 (0.16-0.24)	One dropped ventricular beat— Wenckebach phenomenon (fig- ure 3)
Pressure on left carotid sinus . . .	75	0.27	No dropped ventricular beats
5 min. after administering atro- pine sulphate (1/50 gr.) hypo- dermically . . . . .	103	0.17	No dropped ventricular beats
15 min. after atropine adminis- tration . . . . .	111	0.18	No dropped ventricular beats (figure 5)
25 min. after atropine adminis- tration . . . . .	115	0.17	No dropped ventricular beats
27 min. after atropine adminis- tration; breath held and both carotid sinuses pressed upon . .	91	0.20	No dropped ventricular beats
28 min. after atropine adminis- tration . . . . .	91	0.22	No dropped ventricular beats

8 minims of 1/1000 dilution, physostigmin, gr. 1/30 and mecholyl, 1 mg. to 10 mg., all given subcutaneously, had no effect on the A-V conduction although manifesting their other usual actions.

### DISCUSSION

The observation that such vagus stimulants as deep inspiration, carotid sinus pressure and digitalis all accentuated the heart block, suggested the vagal origin of this heart block. This was confirmed by the complete abolition of the block when atropine was administered. The apparent absence of vagus stimulation by physostigmin and mecholyl is attributed to the observed unpleasantness of their side reactions counteracting the vagus effects. The inability of adrenalin—in contrast to atropine—to alter the A-V conduction also supports the view that the vagus is the mode by which the A-V block is produced and varied. The fainting spells for which the patient was originally referred to us, were most likely due to a more advanced heart block produced by an accentuation, through fear, of his already existent second degree heart block.

The persistence over a period of years of a severe degree of A-V block entirely due to vagus influence, is unusual. Only a few similar cases have been previously reported. In this boy the increased vagal tone manifested itself only on the A-V conduction, since no other evidence of vagotonia was demonstrable. This type of case occurring in a young individual must be distinguished from organic heart block.

## SUMMARY

A 14 year old patient is reported with persistent vagus A-V heart block of marked degree. Atropine abolished the block. The action of certain other drugs and procedures on the block is reported.

It is a pleasure to acknowledge my indebtedness to Dr. L. N. Katz for his helpful advice in the study of this case and in preparing the report.

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## EDITORIAL

### *THE USE OF THIAMIN IN NEUROLOGICAL DISEASES*

The demonstration that the polyneuritis of alcoholic addicts, like that of oriental beriberi, is caused by a deficiency of vitamin B<sub>1</sub> and can be cured by the administration of this substance<sup>1</sup> has aroused wide interest in the possible relation of dietary deficiencies to other types of degenerative diseases of the nervous system. There is strong evidence that a similar deficiency is responsible for the neuritis which may appear in patients on inadequate diets in such conditions as the early toxemias of pregnancy,<sup>2</sup> protracted infections<sup>3</sup> and serious gastrointestinal disturbances.<sup>4</sup>

The successful use of thiamin chloride in the treatment of these conditions led naturally to its trial in types of neuritis and other degenerations which are not associated with any obvious vitamin deficiency. Many articles have appeared during the past three years in both the American and European literature reporting favorable therapeutic results in such conditions. Success has been claimed in diseases which are very diverse in type and etiologically appear entirely unrelated. These include diabetic neuritis, arsenical neuritis, trigeminal neuralgia, and localized neuritis of the brachial plexus and of various individual peripheral nerves; herpes zoster, poliomyelitis, and postdiphtheritic paralyses; retrobulbar neuritis and the funicular myelitis of pernicious anemia; and even the lightning pains of tabes and intractable pains of cancer. In most of these cases thiamin chloride was administered by parenteral injection in large doses, often over a period of several weeks.

Many of these reports are not convincing because the number of cases was small and treatment was not properly controlled. In a few instances, however, careful studies covering a reasonably adequate series of cases have been reported. Thus Vorhaus, Williams and Waterman<sup>5</sup> treated 100 cases of neuritis, of which 22 were cases of localized neuritis and 78, polyneuritis of various types. In only a few of these was there a probable dietary deficiency, but all had pain and most of them were of long duration. Complete relief was obtained in 44 per cent and substantial improvement in 48 per cent more. Similar results have been reported in smaller series of

<sup>1</sup> JOLLIFFE, N., COLBERT, C. N., and JOFFE, P. N.: Observations on the relationship of vitamin B (B<sub>1</sub>) to polyneuritis in the alcohol addict, *Am. Jr. Med. Sci.*, 1936, clxxxixi, 515-526.

<sup>2</sup> STAEHLER, F.: B<sub>1</sub>-hypovitaminosen in der Schwangerschaft, *München. med. Wchnschr.*, 1937, lxxxiv, 327-331.

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cases by Stevenson<sup>6</sup> and by Kühnau.<sup>7</sup> These observers also noted relief of pain in a small group of cases of trigeminal neuralgia and herpes zoster. The results in the other conditions noted seem questionable. Vorhaus and his associates did not attribute the improvement to the correction of a vitamin deficiency but thought it must be ascribed to a "nonspecific" effect of thiamin on neuritis, regardless of its origin.

The results of treatment of the combined sclerosis of pernicious anemia with thiamin have been conflicting. In a series of seven cases, however, reported by Fouts and his associates,<sup>8</sup> which was properly controlled, no benefit was obtained. Although the general condition of the patients was temporarily improved, both the anemia and the sclerosis progressed.

The treatment of selected cases of retrobulbar neuritis with thiamin or with the vitamin B complex has a more secure basis. There is strong evidence that this condition is sometimes the result of a dietary deficiency. Several Japanese observers have noted the frequency with which beriberi is associated with retrobulbar neuritis. In a series of 90 cases, Shimazono<sup>9</sup> found evidence of beriberi in 50 per cent. Typical cases with beriberi have also been reported in this country. Retrobulbar neuritis may also occur in cases of pellagra. Extensive outbreaks have been reported in the tropics among natives who had subsisted on grossly inadequate diets. Thus Moore<sup>10</sup> observed a large number of such cases in Southern Nigeria. In addition to a glossitis, stomatitis and typical scrotal skin lesions, these cases showed a retrobulbar neuritis with a secondary optic atrophy. He found this condition present in 60 per cent of 3,000 individuals examined because of visual defects. Treatment with marmite in the early stages restored normal vision and effected a complete cure.

In this country retrobulbar neuritis and even optic neuritis have been observed in a number of alcoholic addicts with pellagra. Carroll<sup>11</sup> in particular has emphasized the importance of dietary deficiency in producing "tobacco-alcohol amblyopia." In seven of a series of eight cases treated by means of an adequate diet and the administration of yeast, he obtained improvement in vision although these individuals continued to consume their customary quantities of alcohol and tobacco.

These observations are of great significance in indicating the disastrous effects that dietary deficiency may exert on vision and the importance of an early diagnosis in such cases. If treatment was started promptly, vision which had been reduced to counting fingers might be completely restored,

<sup>6</sup> STEVENSON, D.: Vitamin B<sub>1</sub> in the treatment of neuritis, *Practitioner*, 1938, cxl, 301-306.

<sup>7</sup> KÜHNAU, J., SCHROEDER, H., and WOLFF, O.: Einiges über die Anwendung des Vitamins B<sub>1</sub>, *Deutsch. med. Wchnschr.*, 1937, lxxiii, 1407-1409.

<sup>8</sup> FOUTS, P. J., KEMPF, G. F., GREEN, J. A., and ZERFAS, L. G.: Vitamin B intravenously for the treatment of neurological changes in pernicious anemia, *Jr. Indiana Med. Assoc.*, 1932, xxv, 448-451.

<sup>9</sup> SHIMAZONO, J.: B-avitaminosis und Beriberi, *Ergeb. d. inn. Med.*, 1931, xxxix, 1-68.

<sup>10</sup> MOORE, D. F.: Nutritional retrobulbar neuritis (followed by partial optic atrophy), *Lancet*, 1937, i, 1225-1227.

<sup>11</sup> CARROLL, F. D.: The importance of diet in the etiology and treatment of tobacco-alcohol amblyopia, *Arch. Ophth.*, 1937, xviii, 948-962.

whereas in the late stages little improvement was obtained. There is as yet no definite evidence as to which element of the vitamin B complex is concerned. Since retrobulbar neuritis has rarely been noted in endemic pellagra in the Southern States, it seems probable that a deficiency of thiamin plays the principal part in producing the degeneration.

These observations do not indicate that all cases of retrobulbar neuritis or peripheral neuritis are the result of a vitamin deficiency. They in no way lessen the necessity for an exhaustive study of every individual case and of the elimination or proper treatment of any infection, intoxication or other abnormality which may be found. To substitute a prescription or a few hypodermic injections of thiamin for such an examination is gross malpractice.

The extent to which thiamin may be effective in relieving pain in neuritis which is not caused by a deficiency and the validity of the hypothesis of Vorhaus et al. that it exerts a "nonspecific" effect in such cases can be determined only by further studies. These must be carried out on adequately large groups of patients, and they must be much more carefully controlled and more critically evaluated than is the case with most of those which have been reported. There is fairly convincing evidence that thiamin may relieve pain and cause an improvement in the general condition of the patient in some of these diseases. Its indiscriminate use in any painful malady, however, is certain to result in careless examinations and in the neglect of more appropriate treatment as well as in exploitation of the patients.

P. W. C.

## REVIEWS

*Scarlet Fever.* By GEORGE F. DICK, M.D., D.Sc., and GLADYS HENRY DICK, M.D., D.Sc. 149 pages; 21 × 14.5 cm. Year Book Publishers, Inc., Chicago. 1938. Price, \$2.00.

Those interested chiefly in the bacteriological and immunological aspects of scarlet fever will find in this small volume an interesting and concise account of these subjects. There are chapters devoted to the specificity of hemolytic streptococci, to allergy, to anti-bacterial and local immunity, as well as to prophylaxis, symptoms and treatment. The discussion of symptoms is too brief to be adequate and the greater part of the chapter on treatment is devoted to the use of antitoxin. Eight excellent plates are included, showing the results of skin tests and scarlatina manifestations. A valuable bibliography is appended.

J. E. B.

*Diseases of the Nose, Throat and Ear.* By WILLIAM LINCOLN BALLENGER, M.D., F.A.C.S., and HOWARD CHARLES BALLENGER, M.D., F.A.C.S. 1030 pages; 24 × 15 cm. Lea and Febiger, Philadelphia. 1938. Price, \$11.00.

A review of the seventh edition of Ballenger's "Diseases of the Nose, Throat and Ear" shows several valuable improvements in this excellent book. The anatomical descriptions are clear, concise yet thorough, and so well written that one easily gets a good mental picture of both the gross and microscopic structures described. The discussion and outline of treatment, both medical and surgical, are brought up to date and cover the field in an excellent manner. The chapters on Ear, covering the anatomy, functions, diseases and treatments, both medical and surgical, are the greatest improvement in this edition over former ones. The pictures, diagrams and plates are superior to those in earlier editions.

F. B. A.

*Bones: A Study of the Development and Structure of the Vertebrate Skeleton.* By P. D. F. MURRAY, M.D., D.Sc. 203 pages; 19.5 × 14 cm. Cambridge University Press, New York City. 1936. Price, \$2.50.

The book contains 180 pages of text and 10 of references. The greater part deals with the embryonic and post-embryonic features of the bone and joint system and the normal reactions of bone and cartilage to development and function. A chapter is devoted to the processes of adaptation of bone and cartilage following structural changes. In general the book is interesting, but requires concentration. It merits the study of any teacher of bone pathology.

A. F. V.

*Milestones in Medicine.* Laity Lectures of the New York Academy of Medicine; with introduction by JAMES ALEXANDER MILLER, M.D. 276 pages; 19.5 × 13.5 cm. D. Appleton-Century Company, New York. 1938. Price, \$2.00.

This book is one of a series in which are published the lectures given by the New York Academy of Medicine for the layman. Seven lectures are included in this volume, those given during 1936-37.

The following are the subjects and the contributors: I. The Historical Background of Psychiatry, by Smith Ely Jelliffe, M.D.; II. The Mechanisms of Heredity, by Charles R. Stockard, M.D.; III. Medicine at Sea in the Days of Sail, by Karl Vogel, M.D.; IV. The Evolution of the Human Brain, by Frederick Tilney, M.D.;

V. The History of Medical History, by Henry E. Sigerist, M.D.; VI. The History of Leprosy, by Newton E. Wayson, M.D.; VII. The Story of the Glands of Internal Secretion, by Walter Timme, M.D.

The subject matter of the lectures is presented not in a didactic form, but rather progressively as thought was evolved concerning the various subjects. The reader gets an excellent understanding of the background of the topics, and, from a lay standpoint, the selection of the subjects has been extremely well done.

The sections on psychiatry and the endocrine glands are very interestingly written, and Dr. Timme's description of the hyperthyroid individual should appeal to anyone who has had contact with one of that temperament.

In summary, there are presented lectures of medical interest, by experts for the layman, in a very readable form.

F. G. D.

# COLLEGE NEWS NOTES

## 1939-40 NOMINATIONS FOR ELECTIVE OFFICERS

In accordance with provisions of the By-Laws the Committee on Nominations herewith presents the list of nominees for President-Elect and for the First, Second and Third Vice-Presidents for 1939-40. The election of all nominees shall be by the members of the College at its annual business meeting. Nominations may also be made from the floor at the annual business meeting.

Dr. O. H. Perry Pepper, President-Elect, Philadelphia, Pa., will accede to the presidency.

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### *New Nominations*

President-Elect ..... James D. Bruce, Ann Arbor, Mich.  
First Vice-President ..... Allen A. Jones, Buffalo, N. Y.  
Second Vice-President ..... Gerald B. Webb, Colorado Springs, Colo.  
Third Vice-President ..... J. Morrison Hutcheson, Richmond, Va.

Respectfully submitted,

D. SCLATER LEWIS  
HENRY M. THOMAS, JR.  
FRED W. WILKERSON  
DONALD J. FRICK  
JAMES ALEX. MILLER, *Chairman*  
*Committee on Nominations*

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### NEW LIFE MEMBER

Dr. Mortimer Warren (Fellow, 1929), Pathologist to the Maine General Hospital, Portland, Maine, is the latest addition to the Life Membership roster of the American College of Physicians.

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### GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of publications by members are gratefully acknowledged:

#### *Books*

Dr. Frank W. Spicer, F.A.C.P., Duluth, Minn.—one autographed copy, "Trauma and Internal Disease";  
Dr. S. A. Weisman, F.A.C.P., Minneapolis, Minn.—one autographed copy, "Your Chest Should Be Flat."

#### *Reprints*

Rear Admiral Charles S. Butler, F.A.C.P. (MC) U.S.N.—2 reprints;  
Col. A. T. Cooper, F.A.C.P. (MC) U.S.A.—2 reprints;  
Dr. Everett C. Fox, F.A.C.P., Dallas, Texas—1 reprint;  
Dr. Charles M. Griffith, F.A.C.P., Washington, D. C.—1 reprint, by the late Dr. Philip B. Matz, F.A.C.P.  
Dr. I. W. Held, F.A.C.P., New York, N. Y.—1 reprint (in collaboration with Dr. A. Allen Goldbloom, F.A.C.P.);  
Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J.—1 reprint;



Dr. S. A. Weisman, F.A.C.P., Minneapolis—2 reprints;  
Dr. August A. Werner, F.A.C.P., St. Louis, Mo.—7 reprints.

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#### MONTANA SECTIONAL MEETING

The 3rd Annual Meeting of the Montana members of the American College of Physicians was held in Butte, Montana, February 25, 1939, in the medical library of the Murray Clinic.

Among those present were: Dr. H. W. Gregg, Dr. H. C. Watts, Dr. A. L. Gleason, Dr. E. D. Hitchcock, Dr. F. R. Schemm, Dr. A. C. Johnson, Dr. L. H. Fligman, Dr. M. D. Winter, Dr. A. R. Foss, Dr. J. P. Ritchey, Dr. M. A. Shillington, Dr. Charles F. Little and Dr. M. B. Hesdorffer.

The program under the direction of Dr. H. W. Gregg, consisted of papers, presentation of cases and general discussion. Dr. Gregg presented a case of diabetes in an acromegalic who has shown some improvement under insulin although most of this type of case are insulin resistant. Dr. D. H. Gillespie of the Murray Clinic presented a patient with orthostatic hypotension and reported on two others. Dr. R. F. Peterson of the Murray Clinic spoke on autopsy and laboratory findings in a case of chronic nephritis and discussed the differential diagnosis between the kidney of hypertension and chronic glomerular nephritis. Dr. Gregg reported on cases of polycythemia vera and pointed out the dangers in the use of phenylhydrazin in treatment emphasizing the necessity of keeping the patient under constant observation.

At 7:00 p.m. the members adjourned to the Rocky Mountain Café in Meaderville for dinner, after which there was a general round table discussion and the regular business was transacted.

Dr. Louis H. Fligman, Helena, Governor for Montana, was elected President; Dr. M. D. Winter, Miles City, Vice President; and Dr. H. C. Watts, Fort Harrison, Secretary.

In line with the policy of having the meeting in a central part of the State, it was decided to hold the 1940 meeting in Great Falls, the date to be selected before the Annual Meeting of the College.

The Secretary was instructed to communicate with the associate members in Montana, with a view to having one or more of them present papers on this occasion, in addition to a scientific program to be put on at the Great Falls Clinic.

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Under the presidency of Dr. Henry M. Moses, F.A.C.P., the Brooklyn Society of Internal Medicine held its 18th meeting at the Kings County Hospital, February 24. Dr. George A. Merrill, F.A.C.P., presented a case report on the treatment of status asthmaticus; Dr. Henry Wolfer, F.A.C.P., presented a paper on blood sugar curves in cases of coronary thrombosis; and Dr. Henry Feinblatt, F.A.C.P., and Dr. Barnett Alpert presented a paper on hyperthyroidism: pituitary relationship and therapy.

Dr. George E. Anderson, F.A.C.P., and Dr. Henry D. Fearon, F.A.C.P., are Secretary and Treasurer, respectively, of the Society.

Among its councillors are: Dr. Edward E. Cornwall, F.A.C.P.; Dr. J. Hamilton Crawford, F.A.C.P.; Dr. Frank Bethel Cross, F.A.C.P.; Dr. Edwin P. Maynard, Jr., F.A.C.P.; Dr. George A. Merrill, F.A.C.P.; and Dr. George A. Sheehan, F.A.C.P.

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Dr. George Herrmann, F.A.C.P., Professor of Clinical Medicine at the University of Texas, was guest speaker on the opening day of the Mid-South Postgraduate Assembly at Memphis, Tenn., February 14, 1939, his title being "The Treatment of the Commoner Disorders of the Heart."

Dr. August A. Werner, F.A.C.P., Assistant Professor of Medicine, St. Louis University School of Medicine, addressed the Peoria (Illinois) County Medical Society, February 21, 1939, on "The Effect of the Ductless Glands on Growth and Development."

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Dr. Hugo Mella, F.A.C.P., has been appointed Chief of Postgraduate Instruction and Medical Research Division, Medical and Hospital Service, Veterans Administration, effective February 1, 1939.

Dr. Mella was formerly manager of the Veterans Administration Facility at St. Cloud, Minn. His new appointment has taken him to Washington, D. C., where his residence is at 1335 Ingraham St., N.W.

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Dr. M. Fernán-Núñez, F.A.C.P., Milwaukee, Professor of Pathology in the Marquette University School of Medicine, has been appointed Chairman of the Committee on Cancer of the Wisconsin State Medical Society.

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At the annual meeting of the Southern Interurban Clinicians Club which met at Nashville, Tenn. on January 27 and 28, Dr. V. P. Sydenstricker, F.A.C.P., Professor of Medicine at the University of Georgia School of Medicine, presented a paper entitled, "Hemolytic Icterus Following Splenectomy for Thrombocytopenic Purpura." Dr. Sydenstricker was President of the Club during 1938.

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Dr. Warren Coleman, F.A.C.P., has been appointed Professor of Clinical Medicine at the University of Georgia School of Medicine.

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#### ABSTRACT

#### MINUTES OF THE BOARD OF REGENTS

Philadelphia, Pa.

December 18, 1938

The regular autumn meeting of the Board of Regents was held at the College Headquarters, December 18, 1938, with Dr. William J. Kerr, President, presiding and Mr. E. R. Loveland acting as secretary; with the following present:

William J. Kerr, *President*  
O. H. Perry Pepper, *President-Elect*  
James B. Herrick, *First Vice-President*  
Charles T. Stone, *Third Vice-President*  
William D. Stroud, *Treasurer*  
George Morris Piersol, *Secretary-General*  
Walter L. Bierring  
Egerton L. Crispin  
James Alex. Miller  
Francis M. Pottenger  
David P. Barr  
Ernest B. Bradley  
Roger I. Lee  
Sydney R. Miller  
Robert A. Cooke

Ernest E. Irons  
D. Sclater Lewis  
Hugh J. Morgan  
James E. Paullin  
Maurice C. Pincoffs  
Charles H. Cocke  
John H. Musser (General Chairman of the New Orleans Session)

Mr. Loveland, Secretary, read abstracted minutes of the previous meetings of the Board of Regents at New York during April, 1938, the abstract being approved as read.

The Secretary then read the following communications:

1. A letter from the Chairman of the Board of Regents of the American College of Chest Physicians, replying to an inquiry as to why that organization had adopted a corporate name which so closely simulates that of the American College of Physicians;

2. A communication from Dr. Rock Sleyster, Governor for Wisconsin, concurring with the opinion of our Board of Regents that infringements of medical ethics should be first reviewed by local county medical societies;

3. A report prepared by the Executive Secretary relating to the feasibility of obtaining special liability insurance contracts for Fellows of the College, as follows:

"1. Legislation in some States, such as Pennsylvania, precludes any insurance company from making preferential rates to any special group of physicians; the same rates would have to be made available to any internist, whether a member of the College or not.

"2. Liability insurance companies do not find it practical to write 'group liability insurance' for physicians, for every physician must be personally contacted when writing up his policy; the College should not consider the possibility of acting as an intermediary in writing 'group insurance,' or any other commercial transaction. Hence, the plan would not be practical either for the College or for the insurance company.

"3. The greatest differentiation in liability insurance rates at present is based on geographical location, rather than in types of practice. For instance, rates in Pennsylvania are very much lower than in California. Where there are differentiation in liability insurance rates, very detailed policies must be written. In some States such differentiation in rates do not exist, as between internal medicine and surgery, but the policy must be so written that if the insured performs even the smallest number of 'surgical procedures,' even to the emergency opening of an abscess, he must be classified under the rates for surgeons. In Pennsylvania, the liability rate is basic, that is, equal, for all classes of practitioners. Rates and conditions vary so widely over the country that no basic rate for internists the country over could be furnished by any company, either by desire or legality.

"4. *Conclusion.*—It is impractical for the College to attempt any arrangement for liability insurance for its members at this time."

Secretary Loveland also reported that the Chairman of the College House Committee, Dr. O. H. Perry Pepper, had initiated an application for exemption from taxation on the College Headquarters, but that the Committee on Tax Revision had taken adverse action, and that the matter had been appealed to the Courts, and that the Courts had subsequently sustained the Committee on Tax Revision, refusing exemption from real estate taxation on the College Headquarters.

Under new matters, Secretary Loveland reported that President William J. Kerr had appointed the Second Vice-President of the College, Dr. Noble Wiley Jones,

as the official representative of the American College of Physicians at the inauguration of the Royal Australasian College of Physicians at Sydney, Australia, on December 15, and that Dr. Jones was at that time present at said inauguration.

Secretary Loveland also reported that President Kerr had appointed Dr. James H. Means as the official representative of this College at the inauguration ceremonies of President Carmichael at Tufts College, Boston. Secretary Loveland also presented a communication from Dr. Julien E. Benjamin, F.A.C.P., Cincinnati, strongly objecting to the present principles of reducing initiation fees and annual dues of full-time medical teachers; likewise, a communication from Dr. Morris Fishbein, advising that the Board of Trustees of the American Medical Association had recognized the support given by the American College of Physicians to the Standard Classified Nomenclature of Disease, and that the American College of Physicians would be given an opportunity to send a representative at the next conference; also a communication from Dr. Miles J. Breuer, F.A.C.P., Lincoln, Nebr., concerning economic medical conditions; also a communication from Dr. Robert E. Ramsay, F.A.C.P., presenting arguments for dual certification by the various national certifying boards, where physicians are able to qualify for the examinations of more than one board; also a communication from Dr. John Russell Twiss, F.A.C.P., New York City, as a protest to the College accepting papers for its Annual Sessions dealing with medical-economic problems, especially those revealing the attitude of the "Committee of Four Hundred."

President Kerr reported that the profession of California was very grateful to the American College of Physicians, and to other organizations that supported its fight against the Pound Law. The Pound Law had been defeated in California by approximately three to one, and President Kerr expressed the belief that the influence from outside the State, as indicated by resolutions adopted by various organizations, such as the College, had a very important part in defeating that measure.

President Kerr, in speaking on the problem presented by Dr. Benjamin, said in part, "this is a problem that comes up a good many times in societies and clubs in this country, as to whether those on faculties not on strictly full-time service, but who have consulting practice privileges, should pay regular dues, and I believe it would be proper to appoint a committee to discuss this matter and bring in a report, perhaps, in March. There is some justification, I believe, for that criticism, because there are many whose incomes are perhaps sizeable because of consulting practice."

Dr. James Alex. Miller moved that a committee be appointed to review the whole matter of initiation fees and annual dues. The motion was seconded and carried, and President Kerr appointed Dr. James Alex. Miller as Chairman of said Committee, requesting him to choose two other members of the Committee and to bring in a report to the Regents at New Orleans, La., in March.

Dr. George Morris Piersol, Secretary-General, reported the deaths of the following twenty-three Fellows and two Associates since the last meeting of the Regents:

#### *Fellows*

Austin, Arthur Everett.....	Boston, Mass.	August 22, 1938
Bliss, Walter Parks.....	Pasadena, Calif.	November 3, 1938
Chillingworth, Felix Percy.....	Boston, Mass.	June 29, 1938
Davidson, Kallman Meyer.....	Boston, Mass.	July 22, 1938
Fenno, Frederick Leonard.....	New Orleans, La.	July 20, 1938
Jackson, James Allen.....	Danville, Pa.	December 1, 1938
King, Joseph Millen.....	Los Angeles, Calif.	October 7, 1938
Lattimore, Ralston.....	Savannah, Ga.	April 20, 1938
Levyn, Lester.....	Buffalo, N. Y.	June 24, 1938
Marvel, Philip, Sr.....	Bethlehem, Pa.	September 6, 1938
Matz, Philip Benjamin.....	Washington, D. C.	June 25, 1938
McBrayer, Lewis Burgin.....	Southern Pines, N. C.	April 1, 1938

*Fellows*

McGuire, James Joseph.....	Trenton, N. J.	October 11, 1938
McKinley, Earl Baldwin.....	Washington, D. C.	July 28, 1938
McVean, John Aloysius.....	Cleveland, Ohio	May 26, 1938
Miller, George Caplice.....	Seattle, Wash.	April 2, 1938
Neuhaus, George Emile.....	Omaha, Nebr.	May 15, 1938
Newcomb, Arthur Thurston.....	Pasadena, Calif.	July 19, 1938
Patterson, Ross Vernet.....	Philadelphia, Pa.	May 2, 1938
Stevenson, Charles Wm.....	Wichita Falls, Tex.	July 31, 1938
von Deesten, Henry Theodor.....	Jersey City, N. J.	September 1, 1938
Warfield, Louis Marshall.....	Milwaukee, Wis.	September 28, 1938
Withers, Sanford Martin.....	Denver, Colo.	March 8, 1938

*Associates*

Clark, David R.....	Detroit, Mich.	July 3, 1938
Wright, Fletcher Johnston.....	Petersburg, Va.	May 8, 1938

Dr. Piersol also reported the following additional Life Members since the last Regents' meeting:

Arthur T. Newcomb, Pasadena, Calif. (Deceased)  
 George Bruce Lemmon, Springfield, Mo.  
 Eben C. Hill, Baltimore, Md.  
 James Howard Means, Boston, Mass.

President Kerr called for a report of the Committee on the Annals of Internal Medicine by Dr. James H. Means, Chairman. Dr. Means was not present and there was no report to be presented.

Dr. James E. Paullin, Chairman of the Committee on Public Relations, recommended the acceptance of the following resignations (one Fellow and two Associates):

Thomas A. Groover (Fellow), Washington, D. C.  
 Maynard W. Martin (Associate), Cleveland, Ohio  
 Stuart G. Smith (Associate), Medical Corps, U. S. Army

offering the resolution:

*Resolved*, that the resignations of Dr. Thomas A. Groover (Fellow), Washington, D. C., Dr. Maynard W. Martin (Associate), Cleveland, Ohio, and Major Stuart G. Smith, (Associate), Medical Corps, U. S. Army, be accepted.

The resolution was unanimously adopted by the Regents.

On the recommendation of the Committee on Public Relations certain adjustments were made in the annual dues of Fellows or Associates who, because of physical incapacity, had to retire permanently from the practice of medicine.

Also, on the recommendation of the Committee, one Associate, delinquent in dues for two years was dropped in accordance with the regulations of the By-Laws.

Dr. Sydney R. Miller, Chairman of the Committee on Credentials, reported that his Committee had reviewed the proposals of 152 candidates for Fellowship and 238 candidates for Associateship, a total of 390 proposals. Dr. Miller gave the following analysis of the recommendation of the Committee on Credentials:

*Candidates for Fellowship:*

Elect directly to Fellowship .....	27
Advanced from Associateship .....	81
Elect "as of March 26, 1939" .....	10
	<hr/>
	118
Reject .....	5
Defer for further investigation .....	25
Elect Associates .....	4
	<hr/>
	152
	<hr/>

*Candidates for Associateship:*

Elect to Associateship .....	192
Reject .....	33
Defer for further investigation .....	13
	<u>238</u>

Duplicated copies of the list of candidates and the recommended action were distributed to all the Regents for examination, so that they could be carefully scrutinized by the Regents. The following resolutions were unanimously adopted:

*Resolved*, that the following list of 108 candidates be elected to Fellowship in the American College of Physicians as of this date: (This list has already been published in the January, 1939, issue of the ANNALS OF INTERNAL MEDICINE.)

*Resolved*, that the following list of ten Associates be advanced to Fellowship as of March 26, 1939, which marks the minimum three-year Associate term: (This list has already been published in the January, 1939, issue of the ANNALS OF INTERNAL MEDICINE.)

*Resolved*, that the following list of 196 candidates be elected to Associateship in the American College of Physicians as of this date: (This list has already been published in the January, 1939, issue of the ANNALS OF INTERNAL MEDICINE.)

By resolution, unanimously adopted, eight Associates, who had failed to qualify for advancement to Fellowship within the maximum five-year period, as prescribed by the By-Laws, were dropped from the roster.

On the recommendation of the Credentials Committee the following resolution was adopted:

*Resolved*, that Dr. Arthur W. Grace, New York, N. Y., and Dr. Robert H. Riley, Baltimore, Md., be reinstated to Fellowship in the College.

One Fellow and two Associates were dropped from the roster for failure to take up election by payment of the specified fees and dues within one year of date of election, as prescribed by the regulations.

Dr. Hugh J. Morgan, Chairman of the Committee on Postgraduate Education, presented the following report:

#### AMERICAN COLLEGE OF PHYSICIANS

##### *Memorandum from Chairman of Committee on Postgraduate Instruction*

The Committee on Postgraduate Instruction was informed by the President that its duties for the current year were (1) to arrange for courses in postgraduate instruction of two weeks' duration, to be given in several cities in the United States, prior to the meeting of the College in New Orleans; and (2) to accept the invitation of the College of Surgeons to meet with their committee on postgraduate instruction and their Regents to the end that each College might know more of the programs and objectives of the other. It was the expressed hope of the College of Surgeons that the two Colleges could in part at least relate their activities in the field of graduate instruction.

The Committee reports to the Regents that it has arranged courses of post-graduate instruction to be given in Baltimore, Chicago, St. Louis and Nashville, prior to the New Orleans meeting, March, 1939. Detailed statements relative to these courses are attached to this report. The Committee wishes to formally express its thanks to Doctors Pincoffs, Carr, Barr and Youmans, who have planned the courses and will act as course directors.

At a meeting with the Regents of the College of Surgeons in New York, Oct. 16, 1938, at which the College of Physicians was represented by Doctors Pepper, Bradley, and Means of the liaison committees, Doctors Burwell, Capps, Cocke and Morgan of the Committee on Postgraduate Instruction and Mr. Loveland, the College of Surgeons' program of activity in graduate education was revealed. It seems that the standardization of hospitals by the College of Surgeons has been considered a most successful undertaking. The College constitutes itself a body to set up minimum standards which hospitals must meet to gain the approval of the College, these requirements in the main dealing with the organization and administration of the hospital. Hospitals once accredited by the College of Surgeons are inspected at intervals and must demonstrate that they live up to the College of Surgeons' requirements in order to remain on the accredited list. The College of Surgeons maintains a full time organization of several doctors, trained in the technic of making hospital surveys. This program of certification of hospitals by the American College of Surgeons has been expensive—has met with little or no open opposition from organized medicine—has undoubtedly contributed enormously to the improvement of private and public hospital administration and organization and, thus, to improvement in hospital practice. This is viewed by the College of Surgeons as one of their chief contributions in the past.

They are now embarked upon a new venture—this in the field of graduate education. They feel that the College of Surgeons by its requirements for fellowship, and the certification boards, have set up requirements which only a few favored men can meet since hospitals offering such training are relatively few in number. A two-year service as resident surgeon in a hospital is such a requirement. Relatively few hospitals afford opportunity for this graduate work. It is the aim of the Surgeons to organize hospitals now on its accredited list in such a way as to provide this training, which will be given under the direction and supervision of the College. The surgical residency will provide a two to five year course in graduate instruction in Surgery. It will be organized by the College and given by the hospital staff (Fellows of the College). President Crile visualizes the College of Surgeons as a College with its campus in Chicago but with faculty functioning in hospitals throughout the land. The College of Surgeons has the field organization necessary for the administration of such a plan. It has already surveyed a large number of hospitals relative to their qualifications as places for graduate training in General Surgery and the surgical specialties. This survey includes the fields of interest of six of the American Specialties Boards: (1) General Surgery; (2) Obstetrics and Gynecology; (3) Otolaryngology; (4) Ophthalmology; (5) Orthopedics; and (6) Urology. The College has approved, to date, 89 hospitals with an annual output of 393 new surgeons.

The College of Surgeons field workers are asked about graduate training for internists. Interns in Medicine and medical residents want to know who is looking after their needs, who will provide graduate training in Medicine to meet the requirements of the American College of Physicians and the Certification Board. The College of Surgeons sees an opportunity for the American College of Physicians to get into the field of graduate instruction along with them. It offers its organization and suggests that we provide at least one field worker for the surveys, this worker to relate himself to the College of Surgeons organization. It seems probable that

with this token-worker from us, all field workers would study facilities for medical as well as surgical training in the hospitals.

At our New York meeting the liaison committee and the committee on post-graduate instruction of our College considered the following questions in their discussions of the College of Surgeons invitation:

Does the College of Physicians wish to assume the same kind of leadership in the field of graduate instruction (hospital training) in Internal Medicine and the medical specialties that the College of Surgeons is displaying in General Surgery and the surgical specialties?

If so, does it wish to do so in association with the College of Surgeons?

The consensus of opinion of our committees is that this activity in the field of graduate instruction offered great opportunity for furthering the objectives of the College of Physicians. It is generally agreed that the College of Physicians is obligated to see that young men have an opportunity to acquire the training required for admission to the College and for certification, since the College helped define these requirements. Your committees feel, however, that it is a field to which we of the College have no desire to lay claim without knowledge relative to the interests of other agencies—especially the American Medical Association and the Commission on Graduate Education. It has been intimated that the College of Surgeons' efforts in hospital certification and its current effort in hospital graduate training do not meet with the full approval of the American Medical Association. Nor were our committees convinced that we were in a position to undertake active participation in any project which has as its objective the provision of more and better hospital training for internists without answers to the following questions:

1. How many graduates in Medicine want to become certified internists and cannot because of lack of facilities for proper hospital training?
2. How many internists does the United States need on the basis of its present population? And how many more than the country is getting does it need?
3. What contribution will the Commission on Graduate Education make to the problem of graduate education?
4. May there exist another agency better equipped than the College of Physicians to handle the problem of surveying hospitals and determining their fitness for graduate training in Medicine?

What is the optimum number of internists for the United States? One approach to the question is to be found in the Roger Lee-L. W. Jones study of 1933. ("The Fundamentals of Good Medical Care." Publication of the Committee on the Cost of Medical Care: No. 22. University of Chicago Press, 1933). From this study it may be inferred that 6,216 hours of care per one hundred thousand population should be rendered by internists. Dr. R. Buerki of the Commission on Graduate Medical Education writes that, if one accepts the Lee-Jones study and assumes that the average internist works 2,000 hours a year (40 hours a week for 50 weeks), this country, with a population of 125,000,000, needs 3,885 internists. Dr. Buerki points out that the 1936 A. M. A. Directory lists 4,817 men as limiting their practice to Internal Medicine and 566 as limiting their practice to tuberculosis.

What is the annual replacement need for internists? Buerki estimates that the number needed to maintain the figures given in the Directory of the A. M. A. for internal medicine and tuberculosis as 162 replacements annually (this figure assumes that the internist will have 4 years hospital training before embarking upon a thirty-three year period of practice). Using the figures of the Council on Medical Education and Hospitals for 1937-38, Dr. Buerki estimates that at present there are 451 residencies in general medicine, 4 in cardiology, 45 in communicable diseases and 221 in tuberculosis. Buerki points out that many of these residencies are for a



longer period than one year. In this group, however, 329 men complete their residency in general medicine, 4 in cardiology, 45 in communicable diseases, and 175 in tuberculosis each year. If only residencies of 3 years or longer are deemed acceptable, then there are only 143 residencies available in internal medicine and 52 in tuberculosis, with an annual output of 44 and 17 respectively. Buerki points out that, although the number of 3 years + residencies is small, it has increased by over 300 per cent in the past 4 years, and he predicts a more rapid growth for the future than has occurred in the past.

From the above considerations, your chairman is of the opinion that there is no immediate need of a great increase in the number of medical residencies. Unless current surveys indicate that the above estimates of needs are based upon false premises or unless we are to witness in the United States a great increase in the quantity of medical care provided by internists, we are disposed to the opinion that there is no dearth of self-designated and certified internists actually in practice and that the annual replacement needs for this group can be provided by the positions now available (residencies, fellowships) for special training.

*Your committees feel that an immediate contribution which this College could make to the problem of graduate education for internists would be to lend its influence to improving the quality of training which is afforded by medical internships and residencies now in existence.*

This work may be undertaken by the College of Physicians (1) as an independent enterprise; (2) as a joint undertaking with the College of Surgeons; (3) by establishing an effective relationship with the Council on Medical Education and Hospitals of the A. M. A.

The factor of expense possibly would constitute a serious obstacle to undertaking the work as an independent enterprise.

If we join with the Surgeons in their Graduate Education activities and invade the field of Medicine as they have that of Surgery, we must

- (A) (a) Survey hospitals and determine the adequacy of residency positions offered by them for graduate training.
- (b) Furnish criteria by which such hospitals are to be graded. If we are to do this and maintain an equal footing with the Surgeons in the joint undertaking, we should be prepared to survey and furnish criteria for Internal Medicine and, possibly, also for Pediatrics, Dermatology and Syphilology, Neurology and Psychiatry.
- (B) We must be prepared to meet a certain amount of criticism from the A. M. A., whose Council on Medical Education and Hospitals has been engaged in a "comprehensive survey of graduate medical education in the United States," since 1936, and whose studies include (1) apprenticeships, including residencies and fellowships leading to specialization; (2) opportunities for graduate study—i.e., formal courses; (3) courses for practitioners; and (4) extension courses. Dr. Cutter informs us that "it may be found desirable to formulate standards by which the Council could give certain types of instruction definite approval," thus inferring that the Council's present function in this field is chiefly fact-finding (though the Council published in 1936 a statement on "Essentials in a Hospital Approved for Residencies in Specialties," and a list of hospitals approved by the Council for residencies in the specialties is now available).
- (C) By joining with the Surgeons, we would have to meet criticism which is now directed toward the activities of the Council on Medical Education and Hospitals of the A. M. A. and could perhaps with equal propriety be directed toward the College of Surgeons and the College of Physi-

cians; viz., the proposed activities in graduate education are in a field in which the medical schools, American Specialty Boards, public health organizations, state licensing boards and the American Hospital Association also have an interest. Education should be controlled by a group well removed from guild or craft notions or trade-unionism.

- (D) If the College of Physicians finds itself in sympathy with the program of the College of Surgeons and decides to attempt to do for Medicine and the medical specialties what the College of Surgeons is attempting to do for Surgery and the surgical specialties, our College must, in order to maintain a position of dignity and effectiveness in the joint enterprise, pay its way. The cost would be considerable (one or two field workers and a secretary-stenographer).

The third way in which the College may relate itself to the field of graduate training is through a joint effort with the established body of the A. M. A., which is already working in the field: the Council on Medical Education and Hospitals. It is believed that a new impetus might be given to the work of this Council if our College again expressed its interest in this phase of the Council's activities and proffered it coöperation and advice to the end of formulating new standards, criteria, etc. for resident training in Medicine. Through the withdrawal of its approval this Council now has an enforcing or disciplinary power to insure compliance with such new standards as might be set up. This Council, representing the organized medical profession in this country, would thus command and probably obtain the support of the entire profession. It has now the full support of the Committee on Internships of the American Hospital Association.

By officially throwing the weight of our influence behind the Council on Medical Education and Hospitals of the A. M. A., we would align ourselves with a body which is nominated by the President and elected by the House of Delegates of the A. M. A. and on which there is no official representation from medical schools, state licensing boards, American Hospital Association, the American Specialty Boards, etc. This Council is already engaged in a survey of present facilities and has set up criteria according to which it approves residencies for training in the specialties. This phase of the work of the Council is not adjudged to be of the highest order.

An alignment of our College with the Council of the A. M. A. would doubtless be an informal and unofficial one. Since the Council is responsible only to the A. M. A., the extent of the influence of the College would probably depend entirely upon the personal reactions of the Council members. There could hardly be a joint effort between College and Council. Any effort would be an effort of the Council, supported by the College. (In this connection, it is noteworthy that on December 13, 1936, the Regents of the College passed a resolution supporting the Council of the A. M. A. in its program to "develop better training in the field of Internal Medicine and its related specialties.")

### *Recapitulation*

Your committee is wholeheartedly in favor of making an additional contribution to graduate education over and above the present program of postgraduate training represented in our annual meeting and in the formal courses offered by us. We feel that there exists an opportunity to improve the quality of hospital positions now available for graduate training in internal medicine, to establish criteria and define standards for hospitals offering such positions.

The College may follow one of several courses in dealing with this opportunity.

- (1) We may continue to study the problem (better orientation will be possible after the report of the Commission on Graduate Education is complete) and delay action.

(2) We may again offer our facilities and good wishes to the Council on Medical Education and Hospitals of the A. M. A. This may prove no more than a gesture. It would probably cost and accomplish little and, whatever the result, could hardly be expected to reflect great credit upon us, as a College of Physicians' achievement.

(3) We may accept the invitation of the College of Surgeons to join with them in graduate education work, taking over the field of Internal Medicine and, possibly, the medical specialties (through coöperation with the specialty societies and Specialty Boards).

(4) We may take over the problem as an independent enterprise.

The advantages of Course (3) or (4) are these: The College would be rendering a service which is extremely important, and for which the need is urgent; the service would be rendered in a conspicuous way and would reflect great credit upon the College. Against Course (2) it may be pointed out that the College of Surgeons and the Specialty Boards have invaded the field and duplicated some of the work of the Council on Medical Education and Hospitals. This may be interpreted as indicating that there is dissatisfaction and that new leadership is needed and desired in graduate education in the specialty fields. The enthusiastic reception which the College of Surgeons has been accorded by medical graduates desiring special training in surgery would seem to indicate that this is true. That men high in the Councils of the A. M. A. may actually share this feeling is indicated by the fact that its President is active in the College of Surgeons' graduate education program and urges the College of Physicians to relate itself to it.

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Dr. Morgan's report, as well as various conferences that have been held with the American College of Surgeons and the Council on Medical Education and Hospitals of the American Medical Association were discussed at length by President Kerr, Dr. James B. Herrick, Dr. O. H. Perry Pepper, Dr. Roger I. Lee, Dr. Ernest B. Bradley and others. The Executive Secretary was instructed to mimeograph an adequate number of copies of Dr. Morgan's report and distribute same to the members of the Board of Regents for study. The following resolution, proposed by Dr. O. H. Perry Pepper, was seconded and regularly carried:

*"Resolved*, that it is moved that the Board of Regents express to the Council on Medical Education of the American Medical Association, and to the Commission on Graduate Education, its opinion that the American College of Physicians has an inherent interest in the field of graduate training and education; and its desire to extend this interest and its active participation in this field.

"To this end the College requests the Council on Medical Education of the American Medical Association, and the Commission on Graduate Education, to consider how the American College of Physicians can, in their opinion, best move in this direction.

"Further, if it seems desirable to either body that a conference of representatives of that body and of the American College of Physicians be held, the American College of Physicians will be glad to be represented at such conference by its Committee on Graduate Education.

"Further, the expenditure of funds required for representation at such a conference is hereby authorized."

President Kerr said that the Committee on Postgraduate Education will represent the American College of Physicians, whereupon President Kerr appointed Dr. Hugh J. Morgan and Dr. Joseph A. Capps of the College Committee on Postgraduate Education.

Dr. Walter L. Bierring, Chairman of the American Board of Internal Medicine, presented the following report:

"The American Board of Internal Medicine is now in its third year of operation, having been organized July 1, 1936. During the period from July 1 to October 1, 1938, the office of Secretary and Treasurer has been transferred to Madison, Wisconsin, Dr. William S. Middleton having been elected to this office at the last annual meeting in April, 1938, at New York City, succeeding Dr. O. H. Perry Pepper, of Philadelphia. All official correspondence of the Board is now directed through the office of the Secretary-Treasurer at Madison. At this same meeting, Dr. David P. Barr was elected Vice-Chairman to succeed Dr. Jonathan C. Meakins. The Chairmanship remained unchanged.

"Upon the nomination of the Board of Regents, Dr. William S. Middleton was elected for the term ending 1941, and Dr. Louis Hamman for the (unexpired) term of Dr. O. H. Perry Pepper, ending 1941, at the special meeting in San Francisco, June 10, 1938, for membership on the American Board of Internal Medicine as representatives of the American College of Physicians.

"Since its organization, the Board has certified by examination 170 candidates, 56 in 1937 and 114 in 1938. During this period about 1,800 applications for certification without examination were approved. The date limit for considering such applications terminated on July 1, 1937, which was reaffirmed at two subsequent meetings of the Board, but by special motion it was resolved at the annual meeting in New York City, April 6, 1938, that the Board reserves the right to consider special applications for such certification at any time subsequent to July 1, 1937. Since setting a final date for considering applications for certification without examination, the applications for admission to the examination have greatly increased, as indicated by 171 candidates appearing for the written examination held on Monday, October 17, 1938, at different medical centers throughout the United States and Canada. The number of applications already received at the Secretary's Office for the next written examination on February 20, 1939, makes it likely that a similar large number of candidates will appear on that date.

"It will be recognized that the increased number of candidates becoming eligible for the final practical examinations makes the problems concerned with the conduct of such practical tests increasingly difficult. Extra or regional practical examinations, additional associate examiners have been considered, but for the present, the Board has decided to adhere to its present plan of two practical examinations each year conducted by members of the Board in connection with the Annual Sessions of the American College of Physicians and the American Medical Association. As more time will be required, the examination period will probably encroach upon the Sessions of both organizations, but it will be endeavored to interfere with the scientific program as little as possible.

"The Board at its meeting yesterday approved the publication of a registry of certified diplomates which will be ready for distribution within a short time.

"The Board is gratified with the progress made since its organization. Its influence on graduate medical education is evident, particularly with reference to special training in internal medicine.

"The sponsorship of the American Board of Internal Medicine will always be one of the distinctive contributions of the American College of Physicians towards the advancement of internal medicine in America."

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, reported upon the work of some of the past Research Fellows of the College, including Doctors Myron Prinzmetal, who worked under Sir Thomas Lewis, of London; Abner McGehee Harvey, who worked under Sir Henry Dale, of London; and Robert Wallace Wilkins, who worked under Dr. Carmichael, of London. He also reported upon the work of the present Research Fellow, Dr. John Russell Smith, who is at present working with Dr. Anrep in Egypt.

The report showed very gratifying and encouraging results. Dr. Barr pointed out that ordinarily there were two Research Fellows appointed each year, but for the past year but one appointment was made. He therefore said that the Committee desired to recommend to the Regents the appointment of three Research Fellows for 1939-40, and in these appointments to depart slightly from the ordinary purpose, which has been the maintenance for a year of a man of promise to study with a master in the particular field in which he has chosen, without clinical or other responsibilities and without the hindrance of teaching duties. The first candidate nominated by the Committee was Dr. Kenneth Austin Evelyn, of Montreal, twenty-seven years of age, B.S. from McGill University, with highest honors in mathematics and physics. He had been encouraged by Dr. Jonathan C. Meakins, of McGill, to work in physics in the Department of Medicine, and while there became interested in studying medicine and took his M.D. degree at McGill. Dr. Barr read a letter from Dr. John Tate, Professor of Physiology, concerning Dr. Evelyn and his outstanding work. While a medical student, and later an intern at the Royal Victoria Hospital, Montreal, Dr. Evelyn was responsible for the development of the photo-electrometer, which is considered a major advance in the ancillary apparatus to the study of medicine, and on that subject and its application. Dr. Evelyn had published eleven papers, all of merit, some of which Dr. Barr displayed for inspection. Dr. Evelyn had also produced an electrically recording stethoscope. He had been interested in the effect of the blood pressure, heart rate and respiratory rate of normal humans produced by inhalation of ionized air. He further had done research in several other problems. The Committee felt that Dr. Evelyn is a man of unusual ability, and that he probably will figure largely in the field of medicine in North America.

The second nominee fell in an entirely different category—Dr. Harold J. Magnuson, of the University of Southern California; twenty-five years of age; an honor student, both in his academic and medical work; had been thoroughly investigated and considered by the Professor of Physiology at the University of Southern California as one of the best two or three students of that institution in the past eight years. Dr. Magnuson is completing the second year of a two-year internship. While a student, he worked in pharmacology and in physiology on the adrenals and on a special method for the demonstration of urea in pharmacology. This nominee desires to pursue a career in academic medicine, devoting his entire time during the next year to studies now under way with Dr. B. O. Raulston. Dr. Raulston has recently installed a very complete spectograph, has standardized it and is now using it for quantitative determination of minerals in tissues, blood, urine and biological materials, and believes that this field of work has great possibilities, and that the results of such investigations will prove to be of worth in clinical medicine. It was the opinion of the Committee that it is justifiable for the College to encourage research work where it is under good auspices in schools where money for research is largely lacking.

The third nominee by the Committee was Dr. Robert H. Williams, of Nashville; twenty-nine years of age; B.S. from Washington and Lee University; M.D. from the Johns Hopkins University, and internships at Vanderbilt Hospital and Johns Hopkins Hospital; now a resident at Vanderbilt University Hospital. This nominee is the author of thirteen papers, many of which were published in collaboration with other men. He wants to study radioactive iodine and the relation of the thyroid to certain phases of fat metabolism, with Hertz and with Robinson, respectively, at Boston.

On motion by Dr. Barr, seconded and regularly carried, it was

*Resolved*, that the American College of Physicians for the year 1939-40 offer Research Fellowships in the amount of \$1,800.00 each, in accordance with recommendations of the Committee on Fellowships and Awards, to Dr. Kenneth Austin Evelyn, of Montreal; Dr. Harold J. Magnuson, of Los Angeles; and Dr. Robert H.

Williams, now of Nashville; these Fellowships to start July 1, 1939, and extend to June 30, 1940.

Dr. Barr continued with his report as follows:

"The Committee on Fellowships and Awards recommends to the Board of Regents that the John Phillips Memorial Medal for 1939 be awarded to Dr. Tom Douglas Spies for outstanding contributions to the science of nutrition, and particularly for his studies on the nature and character of pellagra.

"Dr. Spies' active studies in this field were begun in Cleveland in 1930. At that time the mortality rate among pellagrins who were treated by the accepted Goldberger dietary regime varied in leading clinics from 50 to 69 per cent, a fact which seemed to indicate either that the Goldberger regime was not therapeutically specific or that the specific substances which it contained were administered in insufficient amounts.

"Between 1930 and 1937, Dr. Spies and his associates were able to demonstrate: (1) that the administration of a pellagra producing diet to pellagrins in relapse is often followed by improvement; that the dermatitis almost always heals on this diet, but that if the glossitis remains unchanged or becomes worse over a period of several days, it serves as an index for testing the potency of a specific therapeutic agent; (2) that vitamin G deficiency of rats (rat pellagra) is different from human pellagra in that a diet identical to that which allows healing of the skin lesions in human beings produces dermatitis in rats; (3) that pellagrins in acute relapse with achlorhydria have the intrinsic factor of Castle in their gastric juices and that consequently pellagra and pernicious anemia are etiologically separate diseases; (4) that pellagra associated with chronic alcoholic addiction was not dependent upon the consumption of alcohol, but was produced by accompanying dietary deficiencies; (5) that pellagra developing secondary to organic disease of the gastrointestinal tract was a form of true pellagra; (6) that the ingestion of diets much higher in calories and much richer in proteins than those previously recommended is desirable in the treatment of pellagra; that an ounce of yeast per day is inadequate for the severely ill pellagrin; that parenteral injections of liver extract in sterile physiological solution of sodium chloride is beneficial. Using diets following these principles, Dr. Spies and his associates were able to reduce the mortality in a series of 125 cases of severe pellagra from 54 to 6 per cent.

"In 1934, through the invaluable aid and coöperation of Dr. James S. McLester, Dr. Spies was able to establish a station for the study and treatment of pellagrins at the Hillman Hospital, Birmingham, Ala.

"In 1935, Dr. Spies became a member of the Department of Medicine of the University of Cincinnati, where through the constant help and encouragement of the Director of the Department, Dr. M. A. Blankenhorn, he was able to continue and extend his observations.

"In 1937, Dr. C. A. Elvehjem announced his observations on the curative effect which was exerted by nicotinic acid in the treatment of black tongue in dogs. This brilliant discovery opened the way for more specific therapy in human pellagra.

"Dr. Spies' first observations with the nicotinic acid treatment were started under controlled conditions in September, 1937, and were announced by Dr. Spies and Dr. Blankenhorn in November, 1937, before the Central Society for Clinical Research. Since that time he and his associates have been able to treat 600 cases of pellagra with only 3 deaths.

"The study of Dr. Spies and his associates during the past few years have indicated that many pellagrins also have beriberi, and that such patients with peripheral neuritis should be considered as cases of beriberi, in which the administration of vitamin B<sub>1</sub> will give relief and nicotinic acid will not. They have also shown that nicotinic acid will relieve mental symptoms and alimentary tract disturbances of pellagra which are not affected by vitamin B<sub>1</sub>.

"Dr. Spies' more recent observations have shown that pellagrins excrete an ether soluble substance, giving the color of porphyrin in 25 per cent hydrochloric acid. Some of this substance has been found to be coproporphyrin I and III. Tests for its determination sufficiently simple for use in a physician's office are of value in detecting clinical cases of pellagra and in showing the effect of treatment with nicotinic acid, which causes the disappearance of the porphyrin-like substances from the urine."

On motion by Dr. Barr, seconded and regularly carried, it was

*Resolved*, that the American College of Physicians award the John Phillips Memorial Medal to Tom Douglas Spies, of Cincinnati, for the year 1939.

Dr. James Alex. Miller, for the guidance of the Finance Committee, determined that it would require a total of \$5,400.00 for these three Fellowships; \$2,700 of which would be required on the budget for 1939, and \$2,700.00 on the budget for 1940.

Dr. William D. Stroud, Treasurer, presented the Treasurer's report concerning purchase and sale of securities, stating that the present holdings amounted to \$100,937.00 in bonds and \$55,637.50 in stocks, at the then present market price. Of this amount, \$67,410.00 in bonds were in the Endowment Fund; \$35,371.95 in bonds and \$57,390.95 in stocks were in the General Fund. All the securities of the College cost \$160,173.33, whereas the present quotations amounted to \$156,575.00, showing a depreciation of somewhat over \$5,000.00. However, many of the securities were purchased several years ago, and it was felt that their value had held up exceedingly well. Dr. Stroud also pointed out that for the year 1938, the College had prospered financially, with an estimated surplus of approximately twenty-nine thousand dollars.

The report of the Treasurer was approved by resolution.

Dr. James Alex. Miller, Chairman of the Finance Committee, reported that that Committee had carefully scrutinized all the statements for 1938 and the proposed budgets for 1939. He distributed detailed copies of all financial reports and of all budget requests and discussed them. The official and final financial statements for the year 1938 will be reported at the Annual Business Meeting of the College at New Orleans in March.

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After a thorough discussion the financial reports and budget requisitions for 1939, the Board of Regents by resolution adopted the budgets for each of the various departments of the College, with an estimated income of \$98,100 and expenditures of \$77,225.

Dr. O. H. Perry Pepper, Chairman of the House Committee, presented a report on the operations of the headquarters building, showing that the operating expenses, as compared with the old offices that were rented, were far less than had been anticipated. Recommendations included the employment of a married couple to act as janitors, instead of the one individual now employed, at an estimated additional cost not exceeding \$400 per annum; the furnishing of a guest room at the College Headquarters, which may be utilized by officers, Regents, Governors, or others, visiting Philadelphia on purely College business. Dr. Pepper also reported that the House Committee had been unable to find a prepared print, engraving or painting to fill the space over the mantel in the College lobby. It had been suggested to the Committee that an artist might be employed to paint a picture of some episode in American medical history, such as for example, the discovery of insulin. The Committee, however, was not agreed that such a proposition is wise, because of doubt as to the availability of an appropriate subject, the uncertainty of the result and the considerable expense entailed on an uncertain result.

By resolution, the report of the House Committee was approved, including an appropriation of \$400.00 for improved janitorial service, and \$250.00 for furnishing the guest room at the College Headquarters.

(*Note:* These additional appropriations increase the 1939 budget to \$77,875.00.) Dr. Roger I. Lee, Chairman of the Committee on Future Policy, reported that that Committee has tried to give a report of progress and nothing more. One of the chief recommendations of the Committee, namely, the establishment of intensive post-graduate courses, is already successfully working. There were several minor suggestions: (1) a request that the College take some interest in the general subject of psychosomatic medicine, which is a new variant of the old term of dynamic psychology; (2) various suggestions in regard to the activity of the College in hospital inspection or operating some sort of Committee to act as a clearing house for individuals to get instruction; (3) a suggestion for forming a library of moving and talking pictures. (The Committee had considered this possibility sympathetically, but did not at the present time feel it feasible from the financial standpoint.)

The Committee had considered at length the question of having the College undertake in a modest way the operation of an information bureau about the opportunities for graduate instruction. The Committee was of the opinion that the College could further develop this activity, and that the Executive Offices can in time become a very active clearing house for information to the College members, in regard to all forms and types of postgraduate training and postgraduate education.

The report was adopted by resolution.

President Kerr reported on details of the program of General Sessions and Morning Lectures for the New Orleans Session, and General Chairman Musser discussed at length plans for the Clinics, Round Tables and Entertainment.

On motion by Dr. James Alex. Miller, seconded and regularly carried, it was

*Resolved*, that the General Chairman shall be authorized to invite members of the Orleans Parish Medical Society to attend the Annual Session of the College as guests, without registration fee, upon presentation of their Parish Medical Society cards.

Furthermore, General Chairman Musser was authorized to arrange a special trip on Saturday following the termination of the New Orleans Session, for those who wish to visit the Leprosarium at Carville, La.

The Executive Secretary, Mr. Loveland, was called upon to discuss any post-convention trips, or cruises, arranged following the New Orleans Session, and he spoke at length concerning the special train to be operated from the East to and from New Orleans; the opportunities for going to or returning from New Orleans by steamship to New York, and the specially conducted tour by railroad to Mexico City, leaving New Orleans on April 1. He expressed regret that it had been impossible to arrange a post-convention cruise to Puerto Rico, in accordance with the unanimous invitation of our Puerto Rico members, due to the fact that no adequate steamship service is available between New Orleans and Puerto Rico.

President Kerr announced that the next meeting of the Committee on Credentials would be held February 26 at the College Headquarters in Philadelphia, and the next meeting of the Board of Regents would be held in New Orleans on March 26.

On motion seconded and regularly carried, it was

*Resolved*, that the College shall defray the expenses of a joint Dinner of the Board of Regents and Board of Governors the evening preceding the opening of the New Orleans Session, and that the discussions shall be centered around matters of policy for the College in which both Governors and Regents may equally engage.

It was further felt that the problem of postgraduate education should be the subject for discussion this year, but that additional reports, such as that made by the Chairman of the Committee on Fellowships and Awards, might also be added.

President Kerr reminded the Regents that two years ago this Board had appointed Dr. William Gerry Morgan as the College Historian, and instructed him to prepare a history up to the time of the New York Session (1938). The original instructions suggested the possibility of a copy of the history being sent to each member



of the College. Dr. Kerr reported that Dr. Morgan's work had almost been finished, and requested the advice of the Regents concerning its publication, estimating that the cost of publication would be from \$1,200.00 to \$1,500.00.

There was general discussion about the possibility of publishing the history in the "Annals of Internal Medicine," or having it first mimeographed and distributed to the Regents.

On motion by Dr. Paullin, seconded and regularly carried, it was

*Resolved*, that action on publication be postponed until the manuscript should be submitted.

Adjournment.

Attest: E. R. LOVELAND,  
*Executive Secretary.*

## OBITUARIES

### DR. JAMES OTHO PARRAMORE

Dr. James Otho Parramore (Fellow, 1925), Medical Director and Superintendent of the Lake County Tuberculosis Sanatorium, Crown Point, Indiana, died at the Billings Hospital, Chicago, from a brain tumor, on January 24, 1939.

Dr. Parramore was born at Hampton, Va., attended the College of William and Mary and graduated from the Medical College of Virginia in 1914. He interned at the U. S. Public Health Hospital in New York City and then became Assistant Physician at the Catawba Sanatorium (Va.) from 1915 to 1916. He then served as Assistant Physician at the Metropolitan Life Insurance Sanatorium, New York, from 1917 to 1919. He served in the Medical Corps of the British Expeditionary Forces in France, from 1917 to 1919, and then returned as Assistant Superintendent of the Iowa Sanatorium, where he remained until 1924. He served for a time as House Physician and Chief of Clinic at the Monroe County (Rochester, N. Y.) Tuberculosis Sanatorium and in October, 1924, became the first Superintendent and Medical Director of the Lake County Tuberculosis Sanatorium at Crown Point, Indiana, which was then being completed, to care for one hundred patients. In 1930 the capacity of this institution was doubled, and a new one hundred bed addition is nearing completion at this time. A chapel is being built in connection with the new addition and Dr. Parramore's funeral was the first service held in it.

Dr. Parramore was President-Elect of the Lake County Medical Society and a member of the Indiana State Medical Association, Association of Military Surgeons and the American Medical Association.

He is survived by his widow, Dr. Grace Parramore, a son, James, age 13, and a daughter, Mary, age 9.

Dr. Parramore was an honored citizen, a competent physician, and his membership was a credit to this College and to other organizations to which he belonged.

O. B. NESBIT, F.A.C.P.,  
*Gary, Indiana*

### DR. CARL BOETTIGER

Dr. Carl Boettiger (Fellow, 1930), Flushing, N. Y., died February 1, 1939. Dr. Boettiger was born June 13, 1879, and received his medical degree from Cornell University Medical College in 1903. He pursued postgraduate study at Harvard University and at Cornell University. He organized the Library at St. John's Long Island City Hospital, and was Director of Pathology there up to a few years ago. During the World War he was in charge of the Base Hospital at Camp Bowie. He was suc-

cessively Assistant Physician and Visiting Physician at St. John's Long Island City Hospital, serving this institution from 1929 to the date of his death. He was also Attending Physician to the Mary Immaculate Hospital, 1929-39; Consulting Physician to the Rockaway Beach Hospital, 1934-39; Attending Physician, Director of Medicine and President of the Medical Board, Queens General Hospital, 1935-39.

Dr. Boettiger effected a coöperation between the New York University College of Medicine and Queens General Hospital, and was appointed Professor of Clinical Medicine at that College in 1939. He was also a member of the Board of Health in the City of New York, 1938-39, and in his earlier experience, 1920-22, he was Assistant Medical Examiner, City of New York.

Dr. Boettiger held many offices in the Medical Society of the County of Queens and directed many of the Committee activities, primarily in matters relating to Public Health. He was President of this Society in 1924, Historian from 1925 to 1939, Editor of its bulletin from 1931 to 1936, and the Directing Librarian from 1936 to 1939. He was President of the Second District Branch of the Medical Society of the State of New York, 1935-36, and a State delegate to the American Medical Association from 1936 to 1939.

In addition, Dr. Boettiger was a Fellow of the New York Academy of Medicine and a member of the American Society of Clinical Pathologists and the American Society of Bacteriologists. He had been a Fellow of the American College of Physicians since 1930 and was a diplomate of the American Board of Internal Medicine. He was President of the Queensboro Tuberculosis and Health Association from 1936 to 1939, and the Honorary President of Queens County Committee of the American Society for the Control of Cancer.

WILLIAM BENENSON, M.D.,  
Acting Directing Librarian,  
Medical Society of the County of Queens

# ANNALS OF INTERNAL MEDICINE

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## OBSERVATIONS ON THE TREATMENT OF LIPOID NEPHROSIS \*

By RALPH H. MAJOR, M.D., *Kansas City, Kansas*

THE disease known as chronic nephrosis or lipoid nephrosis has been the subject of continued dispute since the initial publications of Munk and of Epstein. Opinion still seems to be divided as to whether it is a type of glomerulonephritis or a distinct clinical and pathological entity. There is apparently an increasing amount of opinion favoring the latter view.

In a series of 14 patients, who have been carefully followed since their dismissal from the hospital, all are alive and consider themselves well. All of the 14 show at the present time a normal blood chemistry and are entirely free from edema or any other physical abnormality. Seven of them, however, still have an intermittent albuminuria. These patients have been under observation for periods varying from 10 to two years. What the future course may be would, perhaps, be hazardous to predict. At the present time, however, there is no evidence that would lead one to expect a recurrence of the old disease. The purpose of this communication is to report observations made on these patients with various types of therapy.

In a previous communication it has been pointed out that these patients apparently have an inability to store protein.<sup>3</sup> The observations of several observers, notably those of Collip,<sup>2</sup> indicate that Antuitrin "G" facilitates storage of nitrogen. Because of this fact it was thought desirable to try this method of treatment on a small series of patients.

Figure 1 shows the result of this treatment in one patient, a man, aged 30, who had symptoms of this condition for four months before this observation was begun. The patient received Antuitrin "G" in doses varying from 2 to 4 c.c. daily. No marked response occurred until one month after the injections were begun. At this time there was a marked increase in the total protein, an increase in the serum albumin and serum globulin, and a fall in the blood cholesterol.

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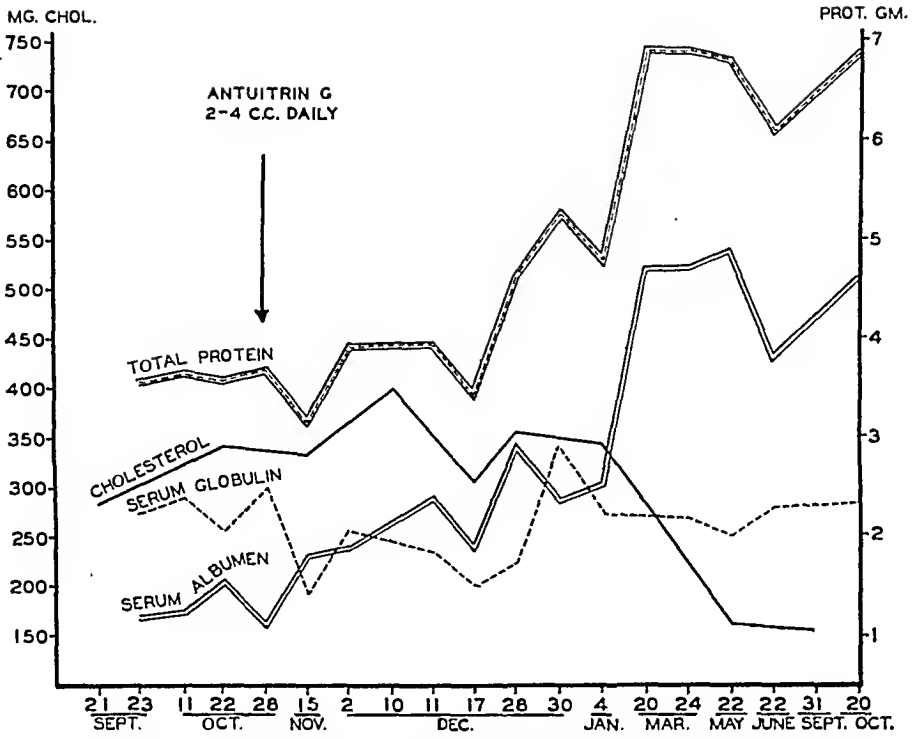


FIG. 1. The effect of the administration of Antuitrin G on the serum proteins and cholesterol in a case of lipid nephrosis.

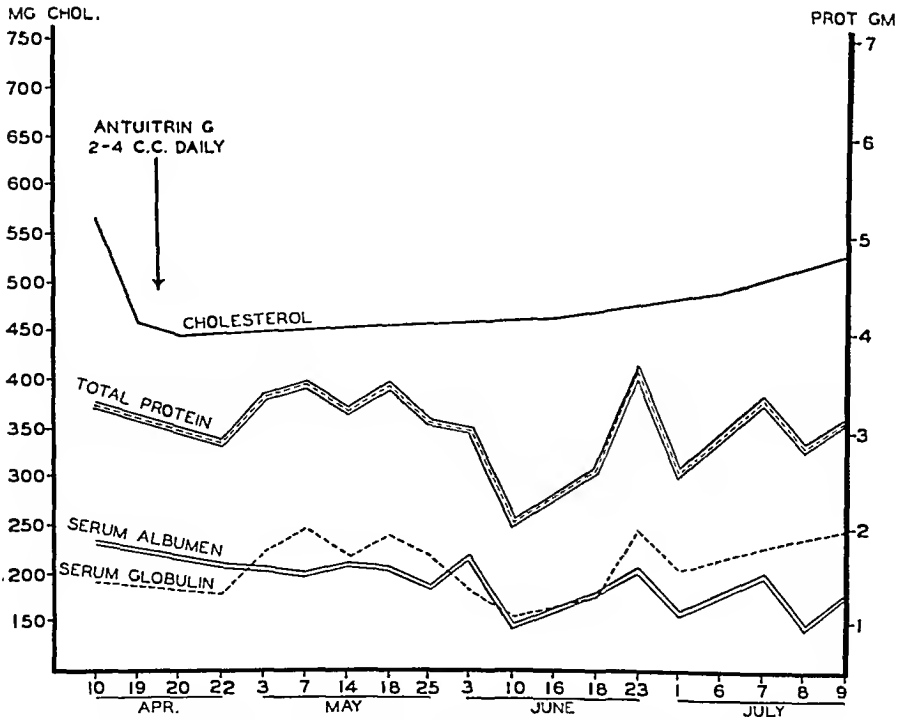


FIG. 2. The effect of the administration of Antuitrin G on the serum proteins and cholesterol in a case of lipid nephrosis.

Encouraged by this result, the same method of treatment was followed in the second patient, a young woman, aged 20, who had been suffering from lipoid nephrosis for two months before this treatment was begun. No marked change in the blood chemistry was noted (figure 2).

The third patient, a man, aged 22, received the same treatment. Again no essential change was noted except the fall in the cholesterol which did not, however, fall to normal value.

Our impression from these observations and two others in which no improvement was noted, was that Antuitrin "G," at least in the doses employed, did not modify the course of the patient's illness. The apparently good result obtained in the first patient was probably due to the beginning of a remission of the disease, since he recovered very rapidly from this point on.

The high blood cholesterol shown by patients with lipoid nephrosis is one of the striking phenomena of the disease. In our experience, as long as the blood cholesterol is high the patient is liable to have a recurrence of edema, low blood protein and marked albuminuria. There is a strong suspicion in the minds of many that the underlying process in this disease is a disturbance in cholesterol metabolism. Until, however, the normal cholesterol metabolism is better understood we cannot hope to have a very clear idea of disorders of cholesterol metabolism. In our two fatal cases of lipoid nephrosis there were extensive deposits of cholesterol in the organs, especially in the liver and kidneys.

Best and Huntsman<sup>1</sup> have shown that the addition of choline to a diet high in fat prevents the deposition of fat in the rats' liver. This observation led us to study the effects of choline on patients with lipoid nephrosis. Five patients in all were studied and all showed similar effects. The observations on two of these patients are shown in figures 3 and 4. In both of these patients the administration of three grams of choline was followed by a preliminary marked rise in blood cholesterol and then a gradual fall. In one of these patients there was a coincident striking increase in the blood protein (figure 3), while in the other the increase was slight (figure 4). In the other three patients there were definite, but no striking increases in the blood protein, such as is shown in figure 3. A preliminary rise of cholesterol after ingestion of choline occurred in all five patients.

Adrenal cortex hormone was administered to four patients without our observing any striking or definite changes. Its administration was suggested by the observations of Thaddea and Fasshauer<sup>4</sup> who found that the administration of this hormone prevented hypercholesterinemia in adrenalectomized animals.

We have continued to obtain the best results, as reported previously, from the employment of a very high carbohydrate diet, varying from 600 to 800 grams of carbohydrate per day. We have also restricted the patient's intake of meat and made the diet as largely vegetable as possible, and in this way reduce the intake of cholesterol containing foods. Eggs are not allowed. We have also added large amounts of soy bean to the

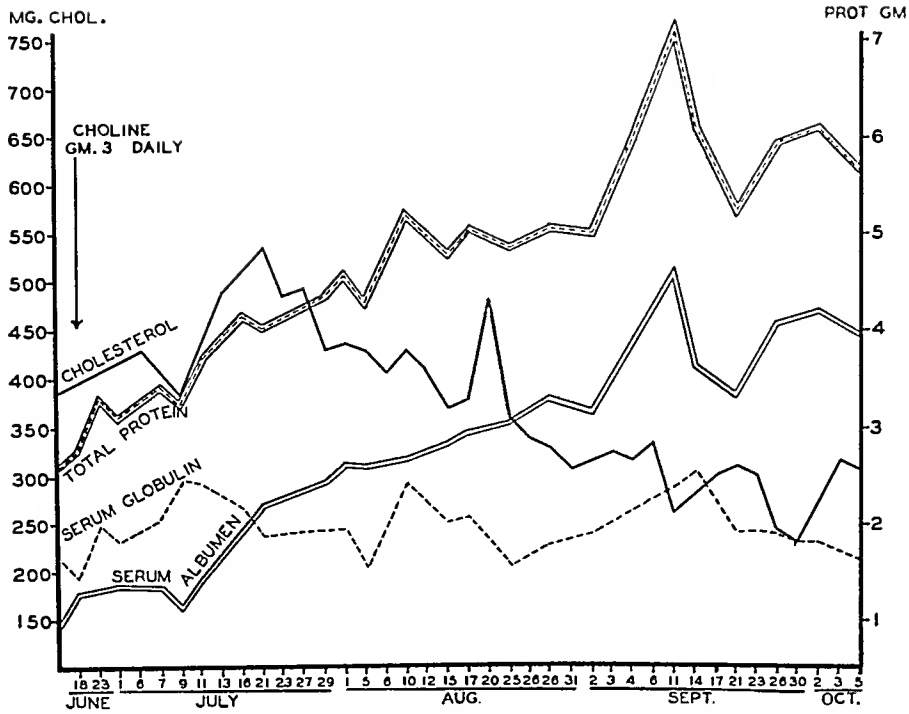


FIG. 3. The effect of the administration of choline on the serum proteins and cholesterol in a case of lipid nephrosis.

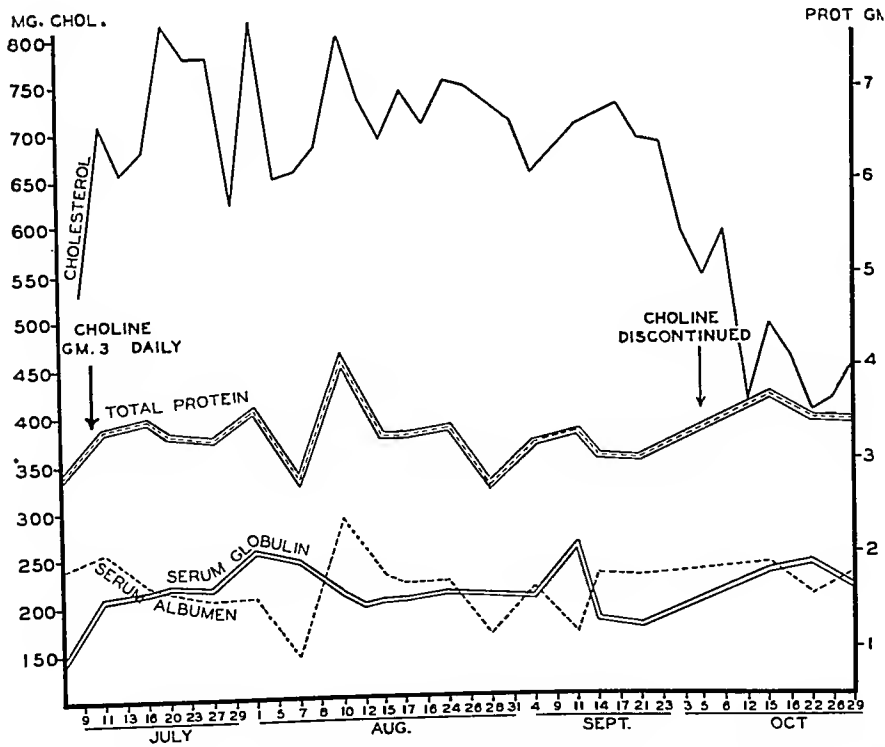


FIG. 4. The effect of the administration of choline on the serum proteins and cholesterol in a case of lipid nephrosis.

diet, but have seen no specific effect upon the regeneration of blood protein. The results obtained in patients on a diet rich in soy beans have not, however, been striking.

### SUMMARY

The administration of Antuitrin "G," choline and adrenal cortex hormone have had no appreciable effect upon the course of lipoid nephrosis. In certain patients the ingestion of choline was followed by a fall in the blood cholesterol values. The best therapeutic results, thus far, have been obtained by employing a high carbohydrate diet combined with blood transfusions and diuretics.

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# THE RENAL THRESHOLD FOR GLUCOSE; CLINICAL OBSERVATIONS ON A CASE OF NON-DIABETIC (RENAL) GLYCOSURIA \*

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THE present day conception of the functional activity of the renal unit has changed the views of the clinician in regard to renal threshold for glucose. It is now believed that the glucose content of glomerular fluid approximates that of the plasma of arterial blood and that in a normal kidney under ordinary conditions, practically all of the glucose is reabsorbed in the first portion of the tubule. The so-called renal threshold is measured in terms of the level of blood sugar at which sugar appears in the urine. Actually, it depends entirely on the functional ability, at any given time, of the tubule to absorb all the sugar from the urine up to the "threshold" percentage amount.

We are presenting in this paper observations on a case of renal glycosuria that throw light on factors which influence the reabsorption of glucose.

## CASE REPORT

R. R., a 39-year-old housewife, was admitted to the medical service of the Johns Hopkins Hospital on March 4, 1937, complaining of sugar in the urine and tumor of the womb. No one in her family had ever had diabetes or any other form of glycosuria. One brother had a small goiter that had never required surgical treatment. The patient was born in North Carolina and had always lived in that state doing the housework on a small farm. At the age of about 12 years, she first became aware of a small goiter which grew gradually in size but never caused any symptoms. When she was 22, her only child was born and thereafter her health was poor. She nursed the child for a year and during that time sugar was found in her urine. After the child was weaned, the glycosuria disappeared. Thyroidectomy was performed and a goiter was in part removed, which, we infer from available history, was colloid and non-toxic in nature. When she was 24, her urine was examined and no mention of sugar was made. Thereafter for five years she felt very well but at the age of 29 the goiter began to reappear and with it she thought there was increased nervousness. When she was 34 she had a severe respiratory infection, but her local physician made no comment after examining her urine. The following year, which was four years ago, when she was 35 years old, she was examined by another physician who reported finding sugar in her urine. She was hospitalized for tonsillectomy and told that her blood sugar was normal. After this the urinary sugar did not increase and it was thought that a low carbohydrate diet had no effect on its amount. She was allowed, therefore, to eat as she pleased. By preference she drank over a quart of milk a day, but otherwise her diet, except that she ate no potatoes, was that of the average Southern woman. She noticed no weight loss, undue sweating or tremor, heat intolerance, or increase in appetite. At no time had there been polydipsia, polyuria, or

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pruritus. Menorrhagia of two years' duration finally led to a diagnosis of myomata uteri and she came to the Johns Hopkins Hospital. Here because of the glycosuria, she was admitted to the medical service.

On admission temperature was 99.0°. Pulse: 86. Respirations: 22. Physical examination showed a rather thin but moderately well-nourished woman who did not appear ill. She was not nervous or overactive, and the eyes gave no evidence of exophthalmos or the associated eye-signs of hyperthyroidism. There was no tremor or undue sweating. No evidence of weight loss or dehydration was made out. There was an old thyroidectomy scar, beneath which in the mid-line lay a nearly spherical nodule about 4 cm. across. Most of this felt as if it were cystic. Throat, lungs and heart were quite normal. The liver edge could be felt just below the costal margin, and in the lower abdomen there was an irregular, firm mass which on pelvic examination proved to be a myomatous uterus. Extremities were normal.

On laboratory examination: Hemoglobin: 82 per cent (12.4 gm.). RBC 3,800,000. WBC: 6,350 with a normal differential. Sedimentation rate: 19 mm. in 1 hour. The urine was acid with a specific gravity of 1.045 and contained 5 per cent sugar (Benedict's quantitative method) all of which fermented with yeast. Three plus acetone was present but no diacetic acid. Albumin and casts were not found in the urine. The blood sugar was 80 mg. per cent (Folin-Wu 1929 method) and the CO<sub>2</sub> combining power was 54.1 vols. per cent. The reducing agent in the urine was shown by Dr. Mary Buell to be entirely made up of glucose; it was completely fermented by ordinary yeast, the osazone formed was a typical glucosazone and the Seliwanoff reaction excluded fructose. The blood Wassermann was negative. Further blood chemical studies included calcium 10.3 mg. per cent; phosphorus 3.9 mg. per cent; non-protein nitrogen 25 mg. per cent; urea nitrogen 12 mg. per cent; total proteins (Kjeldahl method) 6.39 gm. per liter; albumin globulin ratio 63/37; cholesterol on March 8, 492 mg. per cent; on March 17, 469 mg. per cent; and on April 29, 326 mg. per cent; and Van den Bergh, faint indirect trace. Basal metabolic rates varied from plus 19 to plus 6 without iodine treatment. The bromsulphalein test of liver function with 5 mg. per kilo resulted in no retention at the end of 30 minutes. The urine was sterile on culture. The urea clearance test gave a 65 per cent normal standard clearance. Phenolsulphonephthalein test on ordinary fluid intake was 54 per cent in two hours but during a period of forcing fluids to four liters a day was in the neighborhood of 100 per cent.

The diagnoses made were renal glycosuria; recurrent, nodular, non-toxic goiter; and myomata uteri. On March 22, a hysteromyomectomy with appendectomy was performed by Dr. C. S. Stevenson, and on April 17 a cystic adenoma of the thyroid was removed by Dr. P. Kunkel. The second operation was performed purely for cosmetic reasons and the tissue removed was cystic and did not contain any functioning thyroid elements. A postoperative B.M.R. was minus 1 per cent. The patient's rather brief stay in the hospital gave an opportunity for limited metabolic studies.

*Observations:* The patient was placed on a calculated diet with controlled fluid intake and four daily urinary collections, but no therapeutic insulin was given. Repeated blood sugars taken at various times of the day and night were always within normal limits. (See figure 1.) In spite of this, the patient showed a constant glycosuria that varied between 1 per cent and 10 per cent. It is interesting that the urine was never sugar free.

Acetonuria, which was present on admission, disappeared after 24 hours of adequate fluid and carbohydrate intake. It recurred for a short period after each of the operations and following the hysteromyomectomy was accompanied for over a day by a four plus test for diacetic acid.\* The CO<sub>2</sub> combining power, however, never fell

\*The excretion of large amounts of acetone bodies which was observed following both operations, has been noted as a characteristic of renal glycosuria cases by several authors. (Lewis and Mosenthal,<sup>1</sup> Allan and Vanzant.<sup>2</sup>)

below 43.8 vols. per cent and as the patient again became able to take food and fluids, the ketonuria promptly cleared.† The initial high level of blood cholesterol (492 mg. per cent) fell to 326 mg. per cent after 7½ weeks of high carbohydrate intake.

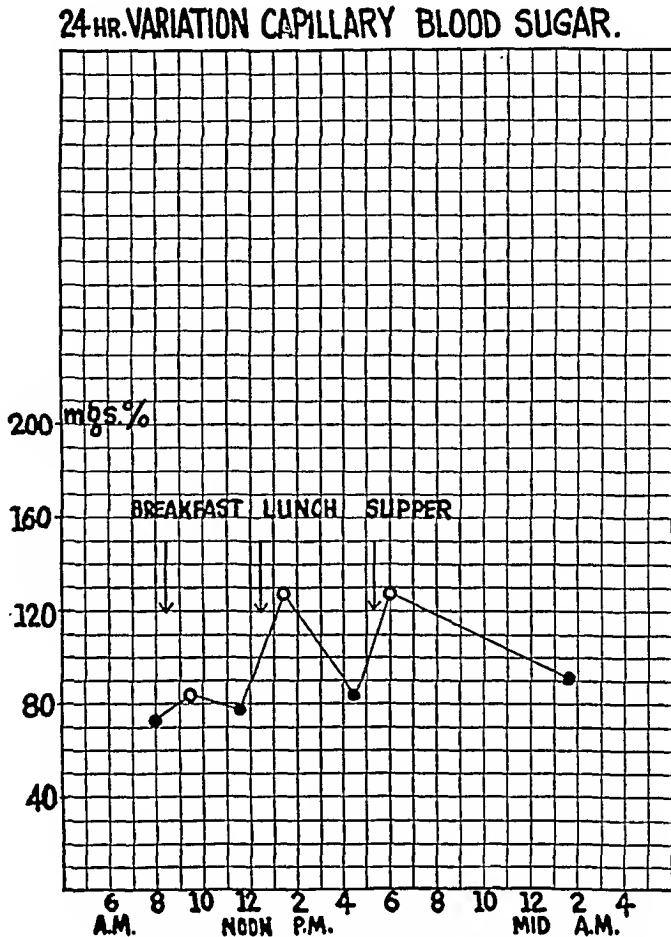


FIG. 1. Twenty-four hour variation capillary blood sugar.

A series of three glucose tolerance tests with simultaneous determinations of the respiratory quotients was performed by Dr. Edward M. Bridge (figure 2). On the initial test the respiratory quotient started at the low fasting value of 0.76 and rose to 0.86. The peak of the blood sugar curve was 218 mg. per cent in capillary blood (Hagedorn-Jensen method) but the venous blood sugar was not determined. A second test 12 days later started at 0.80 and rose to 0.93, and the third, performed after the patient had been in the hospital 38 days, gave high normal values with a rise of respiratory quotient from 0.85 to 0.97, a peak of capillary blood sugar of 197 mg. per cent and a venous blood sugar peak of 156 mg. per cent. Dr. Bridge pointed out that the patient was in a condition of partial starvation at the time of admission owing to the combination of a slight reduction of carbohydrate of the diet and the loss of glucose in the urine. On a high carbohydrate diet (350 gm.) the respiratory quotient curve rose to a high normal. During the third test simultaneous arterial and venous blood sugar (Hagedorn-Jensen method) curves (figure 3) revealed an entirely normal arterio-venous difference<sup>4</sup> (maximum of 41 mg. per cent) and the blood phosphate

† Joslin<sup>3</sup> says, "... ketosis develops during starvation rather than following dietary excesses. . . ."

level dropped from 4.3 to 3.5 mg. per cent, indicating active withdrawal of glucose during the passage of blood through the body tissues.

Two insulin tolerance tests were done by giving the patient two units of regular insulin intravenously. On each occasion there was a prompt fall in the blood sugar

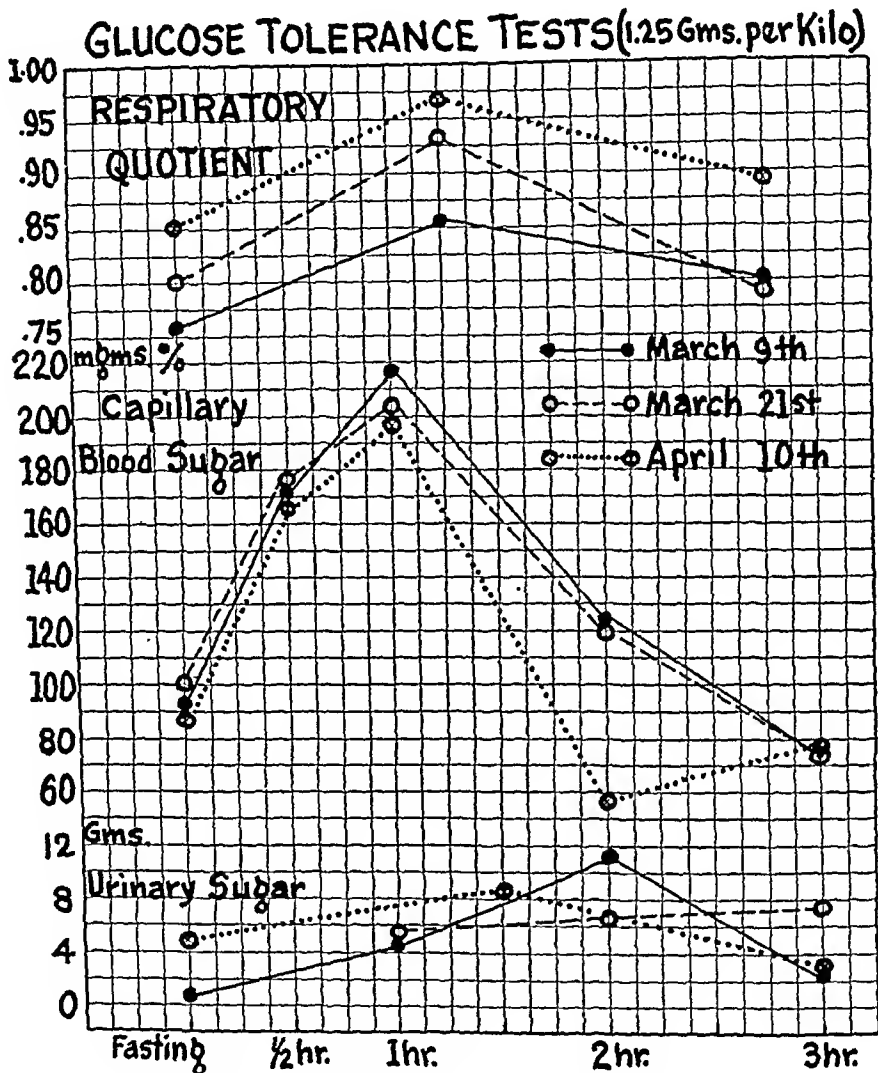


FIG. 2. Glucose tolerance tests (1.25 gm. per kilo.).

level (24 to 25 mg. per cent), indicating a normal sensitivity to insulin (figure 4). Moreover, although the blood sugar fell to 56 and 57 mg. per cent, the sugar did not entirely disappear from any one of the 15 minute specimens of urine. Intravenous insulin, three units before breakfast, and two units before the other two meals, had no apparent effect on the amount of sugar excreted in the urine in one 24 hour period. Three units of insulin intravenously produced marked hypoglycemic symptoms, but unfortunately no urinary or blood determinations were made while these symptoms were present.

On two occasions the patient was given 1 c.c. of pituitrin intramuscularly, while the fluid intake was carefully controlled. The second time the test was performed, while the patient was in a fasting state, there was definite decrease in the urinary output (table 1), but no comparable change in glycosuria. This agrees with obser-

uations by Poulsson<sup>5</sup> and by Burgess, Harvey, and Marshall<sup>6</sup> on the antidiuretic effect of pituitary extract during creatinine and xylose clearance tests. Moreover, the constant glycosuria indicates that neither the glomerular filtrate nor the tubular function of reabsorbing glucose is influenced in man by therapeutic doses of pituitrin.

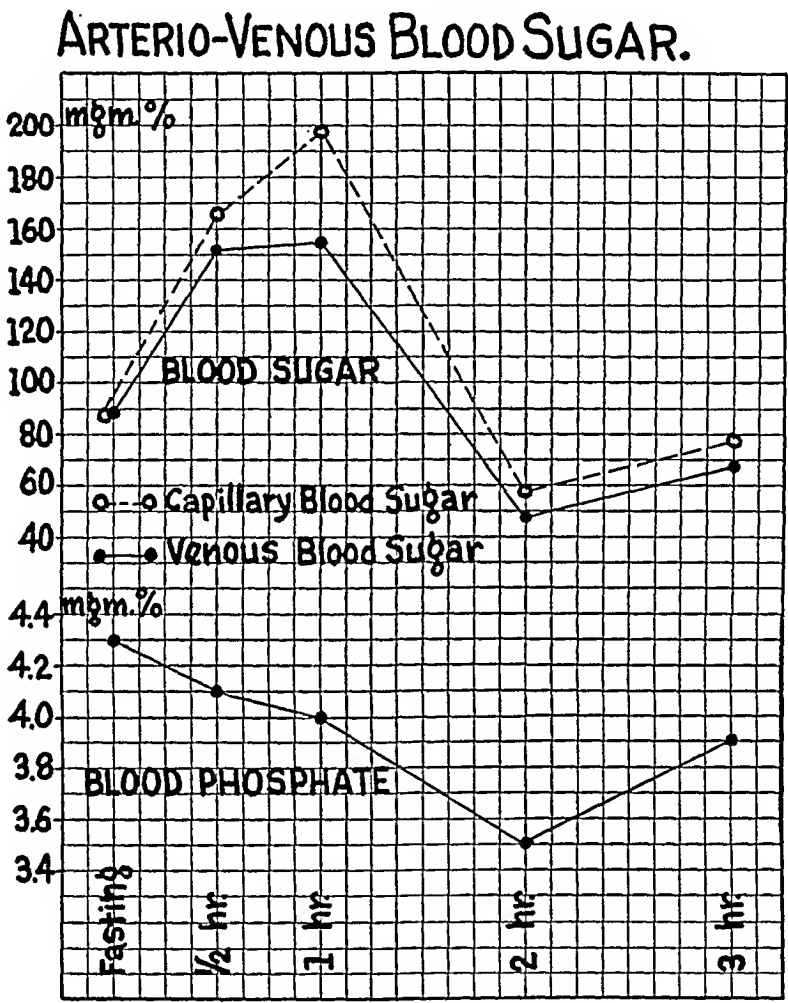


FIG. 3. Arterio-venous blood sugar.

TABLE I  
Effect of Pituitrin on Renal Excretion of Sugar

Time	Fluid Intake	Urine in c.c.	Sugar in gm.	Sugar %
8:00 a.m.	250 c.c.		Specimen discarded	
8:30 a.m.		40	0.42	1.05
9:00 a.m.		100	0.45	0.45
9:02 a.m. Pituitrin 1 c.c. intra-muscularly				
9:30 a.m.	250 c.c.	25	0.36	1.45
10:00 a.m.		13	0.39	3.00
10:30 a.m.		15	0.38	2.50

On April 16, simultaneous urea, xylose, and glucose clearances were performed.\* The results were within the accepted normal variation for urea and xylose and are set forth in table 5. In the two test periods the urea and xylose clearances varied proportionately, the urea clearance being 62.6 per cent of the xylose clearance in period 1, and 60.5 per cent in period 2. The apparent glucose clearance was 40 per cent of the

### INSULIN TOLERANCE TESTS.

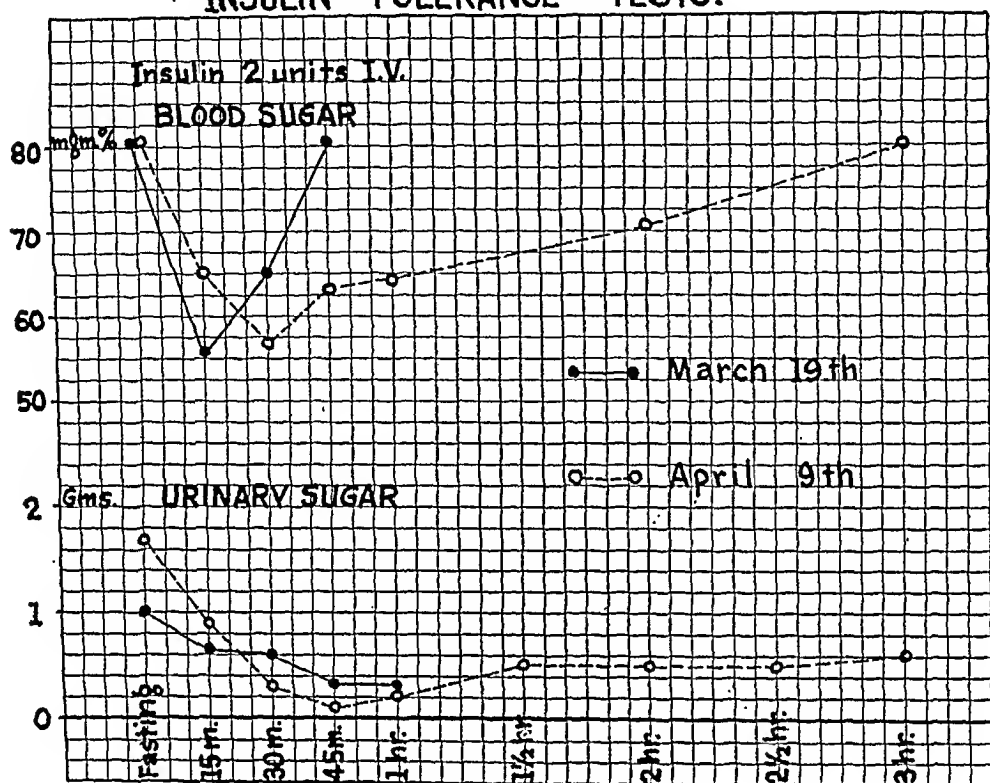


FIG. 4. Insulin tolerance tests.

xylose clearance in period 1 and 49 per cent in period 2. Although no further observations are available and none was made on arterial blood it seems probable that this difference is greater than could be accounted for by experimental error and is, therefore, real. This probability is given credence because of other considerations which will be pointed out in the discussion of the change in daily glucose excretion as affected by water excretion. The work of Homer Smith<sup>7</sup> and his collaborators indicates that inulin clearance is an accurate index of glomerular filtration and that xylose clearance gives figures amounting to about 75 per cent of the inulin amounts and is quite uniform. Recognizing, therefore, that xylose clearance gives results that are too small for the actual filtration figures, we can, however, use the xylose clearance as an index and calculate the amount of fluid and glucose filtered and reabsorbed. The figures are set forth in tables 2, 3 and 4.

We appreciate the fact that no sweeping conclusions can be drawn from these few tests. However, it is worthy of note that the two periods showed a distinct variation in amount of reabsorbed glucose per minute as well as in the percentage of

\* These chemical determinations were performed by Mrs. Margaret White, in the Chemical Laboratories of the Johns Hopkins Hospital. The other chemical determinations reported in this article also were made in these laboratories, except those made by Dr. Bridge, in the Chemical Laboratory of the Harriet Lane Home.

glucose in the reabsorbed fluid. The similarity of the amount of filtered glucose per minute in the two periods is almost surely a coincidence. Why more c.c. of blood should be cleared of glucose when the blood sugar level was 58 mg. per cent than when it was 71 mg. per cent remains to be explained.

TABLE II  
Xylose and Glucose Clearances

	Urine vol. in c.c.	Blood				Urine			
		Reduc- ing sub- stance mg. p. c.	After fermen- tation	Xylose after correc- tion	Glucose after correc- tion	Reduc- ing sub- stance mg. p. c.	After fermen- tation	Xylose after correc- tion	Glucose after correc- tion
Period I	84	200	112	151	71	7400	5300	7080	1310
Period II	96	162	90	121	58	6400	4400	5880	1350

TABLE III  
Comparison of Urinary Concentration of Glucose and Xylose

	Urine vol. in c.c. in 1 hr.	Glucose			True Xylose			c. glucose c. xylose
		in plasma mg. p. c. (Gp)	in urine mg. p. c. (Gu)	Con- cen- tration (C)	in plasma mg. p. c.	in urine mg. p. c.	Con- cen- tration	
Period I	84	71.3	1310	18.3	151	7080	46.8	0.40
Period II	96	58	1350	23	121	5880	48.6	0.47

TABLE IV  
Estimated \* Amount of Glucose That Is Reabsorbed

	Filtered fluid c.c. per min. (F)	Reabsorbed fluid c.c. per min. (R)	Filtered glucose mg. per min. (Fg)	Reabsorbed glucose mg. per min. (Rg)	Glucose mg. p. c. in reabsorbed fluid (Rg %)
Period I	65.5	64.1	46.6	28.3	44.2
Period II	77.7	76.1	45.8	24.2	31.8

$$F = C (\text{Xylose}) \times \frac{U}{60} \quad R = F - U \quad Fg = F \times Gp \% \quad Rg = Fg - \frac{U \times Gu}{100}$$

\* These calculations are based on the xylose clearance figures which have been shown by Homer Smith and his collaborators to be about 75 per cent of the inulin clearance which is thought to be an accurate index of glomerular filtration.

TABLE V

Comparison of Simultaneous Urea, Xylose, and Glucose Clearances\*

	Urea clearance c.c. of blood	Xylose clearance c.c. of blood	Glucose clearance c.c. of blood	Urea clearance Xylose clearance	Glucose clearance Xylose clearance
Period I	41.3	66.2	25.8	62.6%	40%
Period II	47.2	78.0	38.2	60.5%	49%

\* The difference between the blood sugar in venous and arterial blood probably should be taken into account but at low values is thought to be negligible.

On two occasions forcing fluids, the diet remaining constant, greatly augmented the glycosuria while restricting the fluid intake diminished it. Thus from March 14 through 16, with a daily intake of 1,050 c.c. the 24 hour outputs of urinary sugar were 25, 43 and 30 gm., while on the succeeding two days with intakes of 3,900 and 3,800 c.c., 80 and 112 gm. of sugar were lost. Again from April 1 through 4, on an average fluid intake of 3,990 c.c., the average daily glycosuria was 73 gm., while from April 5

## INFLUENCE OF FLUIDS ON GLYCOSURIA.

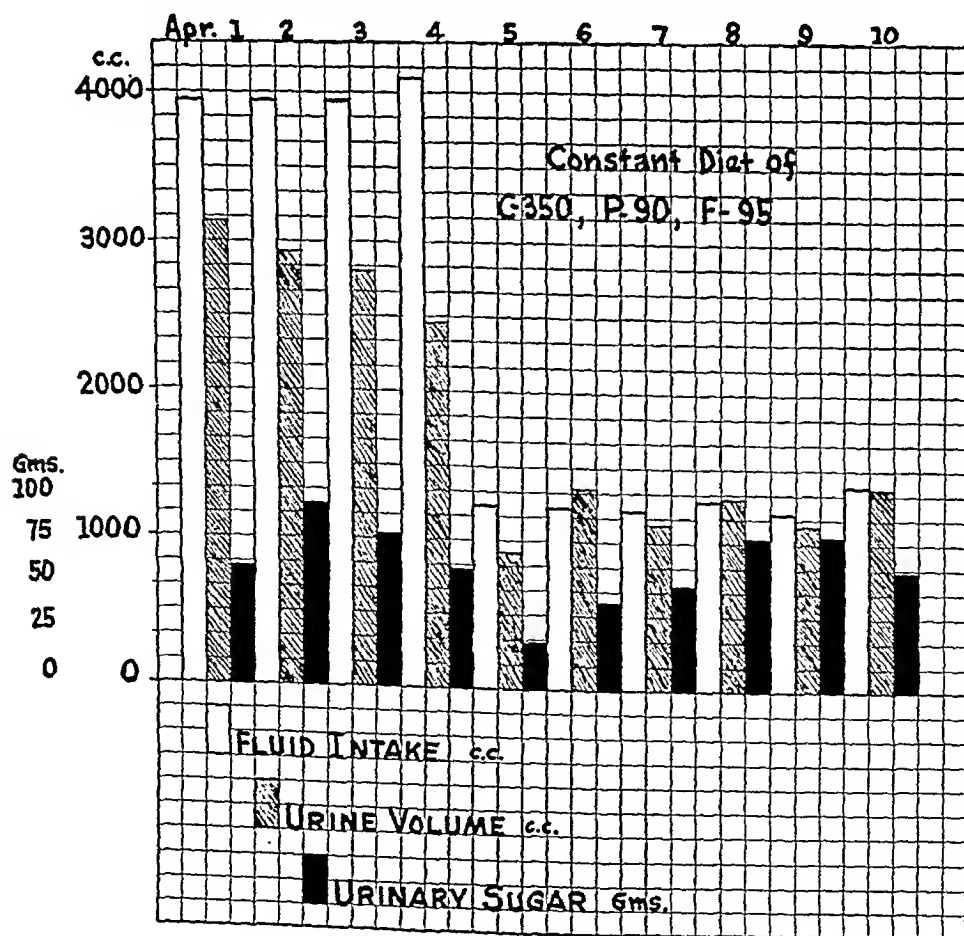


FIG. 5. Influence of fluids on glycosuria.



through April 10, with an average intake of 1,260 c.c., only 56 gm. on the average were spilled daily (figure 5). These changes were simultaneous with the sudden alteration in urinary output, but it is interesting that sustained reduction in the 24 hour urinary output failed to maintain a reduction in 24 hour sugar output. Thus from the second to the fourth day of forced fluids the sugar output declined progressively while after

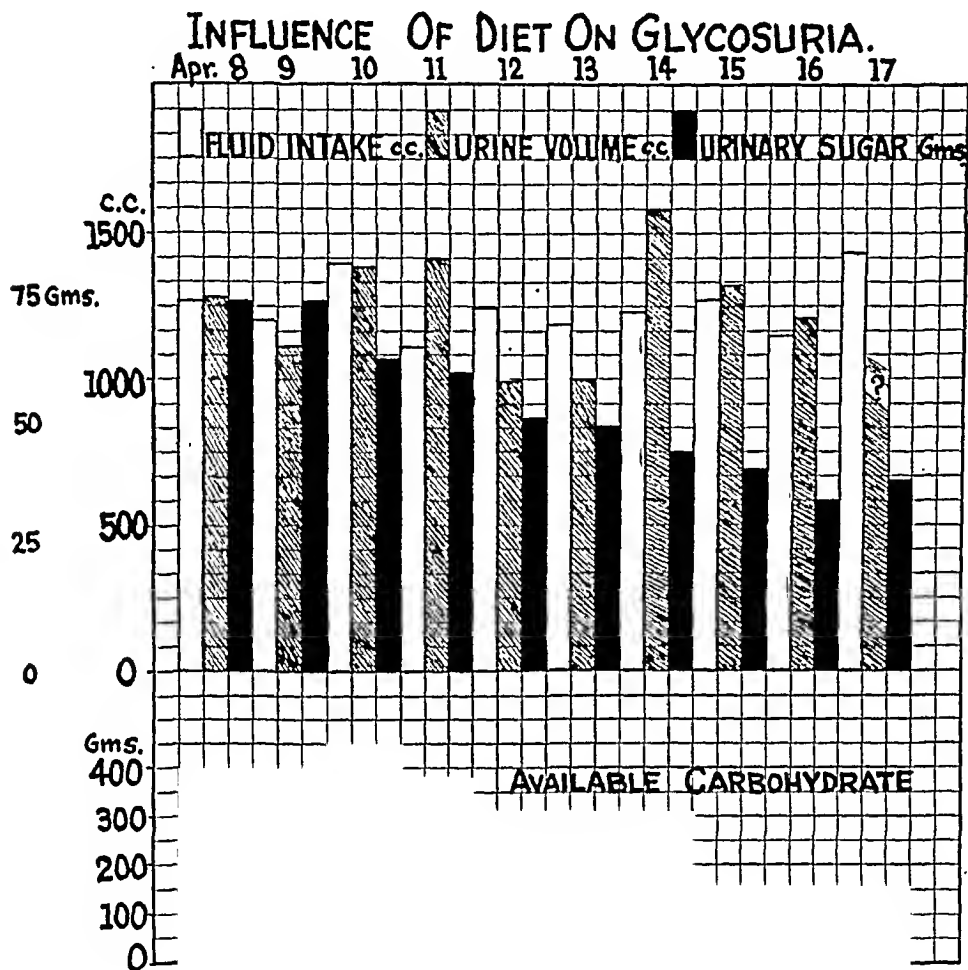


FIG. 6. Influence of diet on glycosuria.

the fluid intake had been sharply curtailed the output of sugar fell abruptly and then rose steadily to the average level. This secondary adjustment was of sufficient magnitude to obliterate entirely the initial effect so that on the third and fourth days of forced intake about the same amount or even a little less sugar was excreted than on the fourth and fifth days of restricted intake. With fluids restricted and the urinary output remaining fairly constant, this secondary adjustment obviously was expressed in a change in percentage of urinary sugar which gradually rose to a figure (10 per cent) which permitted the same amount of sugar to appear in the urine as when fluids were not restricted.

An attempt was made to alter the glycosuria by changing the carbohydrate intake while maintaining the fluid intake constant at 1,200 c.c. a day (figure 6). From April 5 through 10 on a diet of COH 350, P 90, and F 95 (402 grams of available COH by formula of Palmer and Ladd<sup>8</sup>) the average sugar loss was 57 grams.

From April 12 through 14 on a diet of COH 275, P 80, F 125 (321 gm. of available COH) the average loss was 48 gm. And from April 15 through 17, when the diet was COH 110, P 90, F 195 (162 gm. of available COH) the daily glycosuria averaged only 40 gm. These figures indicate that the carbohydrate intake had a slight but definite influence on the glycosuria.<sup>1, 8</sup>

The effect of a salt-free diet was also tried (figure 7). After a six day control period with salt as desired, the patient's diet, for four days, was made nearly salt-free, but without changing its food content or the fluid intake. A slight diuresis resulted

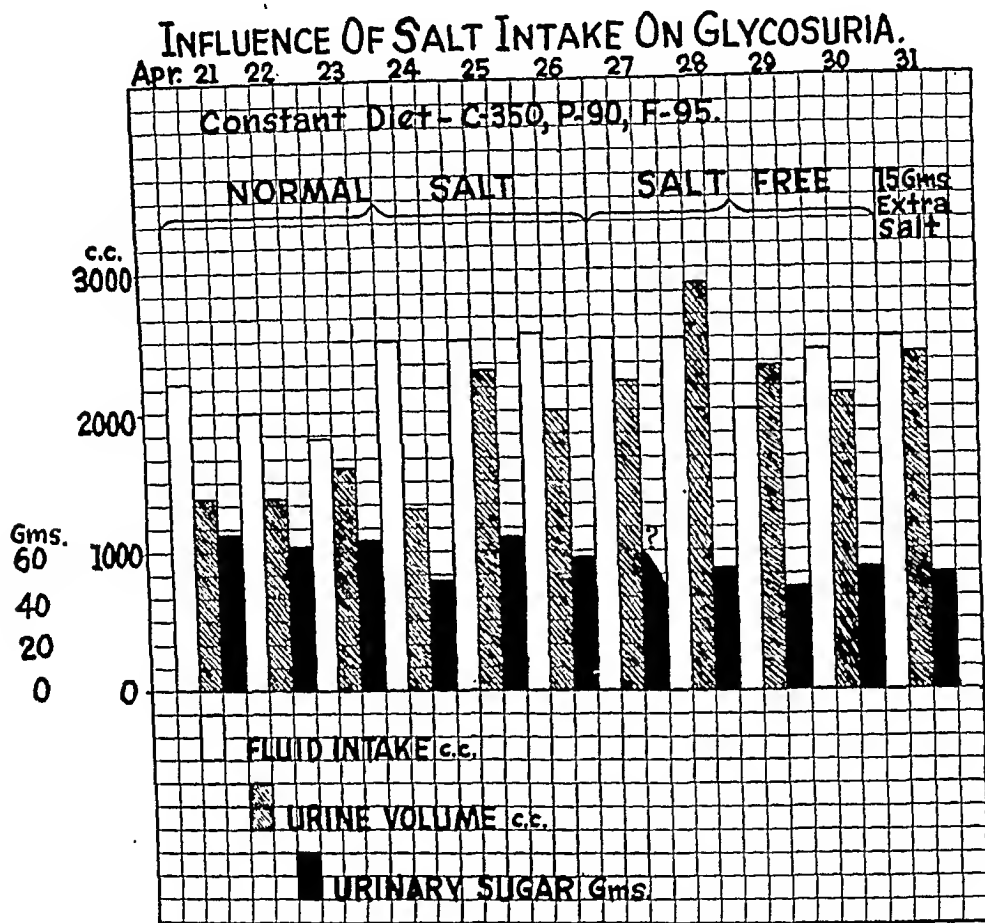


FIG. 7. Influence of salt intake on glycosuria.

which raised the average urinary output from 1,660 to 2,360 c.c., but in spite of this, the average glycosuria fell from 60 to 48 gm. This slight change seems hardly enough to indicate a reduction in the glomerular filtrate or an increase in tubular absorption of sugar during the process of conserving the bodily salt but it points to another factor which must be controlled in experiments on glucose-water balance. Studies of the effect of ingesting excess salt were cut short by the patient's return home, but, on one day of ordinary diet augmented by 15 gm. of salt, the sugar in the urine was unchanged (50 gm.). In short experiments Roch, Martin and Scic-lounoff<sup>10</sup> noted a reduction in glycosuria when hypertonic salt solution was added to the slowly injected glucose solution but our experiments extending over days instead of hours are not comparable to theirs.

## COMMENT

This case conforms to the criteria of true renal glycosuria. (*a*) The reducing substance in the urine was glucose. (*b*) The glucose tolerance curve was normal and at no time during the 24 hours did the blood sugar rise above 156, although Joslin puts the normal post-prandial limit at 170 mg. per cent. (*c*) The respiratory quotient revealed a normal utilization of glucose in the body, as did the fall in blood phosphate during a glucose tolerance test. (*d*) The patient gave no history of symptoms suggesting diabetes mellitus.

Many of the old criteria for the diagnosis of renal glycosuria can now be ignored.<sup>9</sup> In the first place whether or not glycosuria is constant depends purely on whether the blood sugar falls below the renal threshold at some time in the day. Since this depends on the height of blood sugar in relation to the threshold point and indicates a quantitative rather than qualitative difference, it seems useless to make such an arbitrary rule. In the second place, the carbohydrate intake does influence every case to a certain extent. This is graphically demonstrated in our patient by an increase in urinary sugar during glucose tolerance tests and a decrease after intravenous insulin (figures 2 and 4). Moreover, in patients whose carbohydrate metabolism is quite normal, as it was in ours, the amount of carbohydrate in the diet has little effect on the usual 24 hour blood sugar curve. It will be noted that in our case there was a definite but slight reduction in the amount of sugar excreted when the available carbohydrate in the diet was reduced from 402 gm. to 162 gm. (figure 6). This probably depends on a post-prandial variation in blood sugar level which constitutes a definite but small percentage of the 24 hour period of sugar excretion. In the third place, whether or not the individual subsequently develops diabetes mellitus<sup>11</sup> seems to us to have little to do with the diagnosis of non-diabetic glycosuria at any given time. Further facts are necessary before we comprehend the part played in the bodily economy of carbohydrates by the renal threshold.

## DISCUSSION

In a group of 25 healthy male medical students, Campbell, Osgood and Haskins<sup>12</sup> found "The renal threshold for true sugar varies from 99 to 228 mg. per hundred cubic centimeters, 80 per cent of cases having values that range from 140 to 190 mg." The subjects of their investigation ingested 500 c.c. of 50 per cent glucose, voided every five minutes and when the urine became positive for sugar, blood was drawn from the vein. Since the appearance time of glucose in the urine varies after intravenous injection from three to eight minutes (Robinson, Derivaux and Hewell<sup>13</sup>), and since they report that it took five minutes to determine a positive test and draw blood, and since the subjects voided only every five minutes, there was an experimental lag of 8 to 18 minutes. The blood sugar curve was rising during their observations and therefore even these values are somewhat too high.

In the light of these facts, it is not surprising that one occasionally encounters innocent glycosuria in individuals whose low renal threshold is surpassed by their blood sugar level.

In our case, the renal threshold was not accurately determined since 15 minute specimens of urine contained sugar even after the blood sugar had fallen to 56 mg. per cent. Since the observations of Hamman and Hirschman<sup>14</sup> in 1917, it has been thought that the renal threshold for sugar is lower once the secretion of sugar has begun. We believe that this difference in the appearance threshold from the disappearance threshold is more apparent than real and depends largely on the lag in observation time. However, Robinson, Derivaux and Hewell (1935) and Roch, Martin, and Sciclounoff (1936) believe that their observations confirm it. The threshold in our patient, therefore, might have been definitely higher than 56 mg. per cent if we had been able to lower the blood sugar to a point where no more sugar appeared in the urine and then to determine in the usual manner the threshold point at which sugar first made its appearance during the rise in blood sugar. We make this comment merely to point out the fact that the threshold in our patient is not to be compared with that of individuals in whom it is determined from a starting point of a urine which is free of sugar. In this connection, it is equally important to remember that arterial blood sugar values are the ones to be used in determining renal threshold since the blood in the glomerular capillaries is arterial. The difference between capillary whole blood sugar and arterial plasma sugar values is too negligible to warrant consideration (Olmsted<sup>15</sup>). At the fasting blood sugar level there is little difference between arterial and venous sugars, so that in cases with low thresholds these figures are much the same. As the blood sugars rise, however, the difference is increasingly great (figure 3) and in cases with higher thresholds this becomes an important factor which must be considered.

There has been much speculation as to whether or not the threshold changes in a given individual. Knud Faber<sup>16</sup> has paid much attention to the subject of renal threshold for glucose and he states that "the glycosuric threshold in diabetics just as in non-diabetics, has a constant value in one and the same individual, whereas in different individuals it may vary somewhat." However, Faber recognized the significance of the frequent occurrence in pregnancy of glycosuria with normal blood sugar. He studied two women during and after pregnancy. His method was to determine in the course of a glucose tolerance test, the point at which sugar appeared in the urine and then observe the height of the blood sugar. A week later, he administered a smaller dose of glucose and determined the highest blood sugar level obtainable without any glycosuria. This method allowed him to place the threshold below one point and above another. By these means he showed that the threshold rose some months after parturition from below 132 to above 197 in one case and from below 132 to above 150 mg. in the other. Williams and Wills<sup>17</sup> publish a great many glucose

tolerance tests on pregnant women in the early and later parts of pregnancy and following delivery. From these they conclude that ". . . the lowering of the renal threshold, though a factor in all the glycosuric cases, is not the major one in its causation of the glycosuria of pregnancy, but rather it is the association of the lowered threshold with an abnormally raised blood-sugar curve. Only 4 out of 21 cases of glycosuria were simple renal leaks . . .".

It may not profit us to speculate as to the nature of the change in renal threshold which accompanies the temporary endocrine and hormonal imbalance during pregnancy.<sup>19</sup> It does seem cogent, however, to point out the fact that since the renal threshold for glucose depends on the function of the kidney tubules, there may be some association with the disturbance in water balance often encountered in pregnancy in which the kidney tubules, and the effect of posterior pituitary extract on them,<sup>6</sup> play a part. The pituitary alteration which occurs during pregnancy may account for the pregnancy drop in renal threshold.\*

We have no complete explanation for what occurs when there is an abrupt change in the water balance. When the daily fluid intake was increased from 1 liter to 4 liters, the sugar in the urine rose from 30 to 112 gm. In our second experimental period, however, we noted that on a constant fluid intake (4,000 c.c.) and a constant diet (available carbohydrate 402 gm.), the urinary sugar, having first risen, fell on successive days from 92 gm. to 76 gm. to 61 gm. Conversely when the fluid intake was suddenly restricted to 1,200 c.c. a day, the urinary sugar fell to 25 gm. and then rose to 46 gm. to 52 gm. to 77 gm. To know just how the tubules were functioning on each of these days, we would first have to know how much glomerular fluid and glucose were being filtered. This might be learned by frequent glucose and xylose or inulin clearance tests.<sup>7</sup> Then if the glucose clearance varied differently from the inulin clearance, one could infer a change in tubular glucose absorption or, in other words, a temporary change in renal threshold. Without this information we cannot fully comprehend the change in excretion of sugar caused by large changes in fluid intake. Some of the variable factors are (*a*) the height of the blood sugar, (*b*) the amount of glomerular filtrate, (*c*) the amount of water reabsorbed by the tubules, and (*d*) the amount of sugar reabsorbed by the tubules.

On an absolutely constant diet and constant exercise regime, one would expect the blood sugar in a normal individual to behave in a constant manner even under the conditions of sudden change in water balance. In our patient the amount of glucose lost in the urine might tend, if anything, to lower the blood sugar level during the period of forced fluids.

\* In discussing our observations and deductions with Dr. Gerty T. Cori<sup>18</sup> she showed one of us charts setting forth results obtained in experiments she had just performed on normal and hypophysectomized rats. These experiments were devised to elucidate the effect of epinephrine on muscle glycogen, blood sugar and glucose tolerance in normal and hypophysectomized rats. To our great interest the hypophysectomized rats developed higher blood sugars with, at the same time, decreased amounts of sugar in the urine. We agreed that this gave added credence to the theory that the renal threshold for glucose is in some way influenced by pituitary activity.

The amount of glomerular filtrate is known to be tremendously in excess of the actual urine excreted, being 50 to 200 times greater,<sup>20</sup> depending on the amount reabsorbed by the tubules. It is known to vary only under certain unusual conditions. Richards has shown that in frogs only a certain number of glomeruli function at any one time. Under the action of adrenalin all but 5 per cent may close down temporarily and under caffeine they may all open and function simultaneously.<sup>21</sup> Changes in blood pressure and blood flow through the glomeruli alter the amount of filtrate to some degree but on the whole there is surprising constancy. Even during water diuresis<sup>20</sup> the amount of glomerular filtrate remains essentially unchanged and, as in our experiments, with a daily fluid intake neither inadequate nor excessive and with the patient at rest on the ward, the amount of glomerular filtrate probably was more or less constant.

The amount of fluid reabsorbed by the tubules does vary enormously under ordinary diuretic or anti-diuretic influences. The anti-diuretic action of pitressin in man, for instance, is due to a local stimulation of water reabsorption in the thin segment of the loop of Henle.<sup>9</sup> Similarly, water diuresis depends on lessened reabsorption.\* The modern conception of diuresis suggests hormonal control of tubular function even to changing the iso-electric point of the tubules.<sup>21</sup>

The tubular function of reabsorbing sugar is, in average human beings, well in excess of the maximum demands. The question arises as to whether, in an individual with a low renal threshold, this tubular function can be shown to be constant or variable.<sup>23</sup> Our evidence is incomplete but points to variation. Thus we see that when fluids are suddenly restricted the urinary output falls as does the sugar output. In the succeeding days the fluid intake and output remain constant but the sugar increases steadily until the usual level of sugar in the urine is reached. This can occur by a gradual daily increase in the amount of glomerular filtrate or by a gradual reduction in the reabsorptive function of the tubules for glucose. The current belief is, as Poulsson<sup>5</sup> said, that the glomerular filtrate remains fairly constant, and even if we try to explain the rise from 25 gm. to 77 gm. by change in amount of glomerular filtrate, there would have to be an unheard-of three-fold change with, at the same time, a three-fold increase in water reabsorption. Thus we are forced to conclude that the change occurs in the glucose reabsorptive function of the tubular cells. This problem was considered by Poulsson in working with phlorhizin. He says: "It has been a matter of some dispute (Loewi,<sup>12</sup> and Weber<sup>21</sup>) whether a superimposed diuresis increases the sugar elimination in phlorhizin diabetes. This, of course, depends on whether the extra diuresis is accompanied by changes in the rate

\* In the experiments reported in this paper variations in amount of urinary sugar took place at times independently of any change in amount of urine (figure 5) although on restricted fluids the daily urine output was constantly somewhat in excess of the expected amount. During the period of salt free diet the water output was increased but the sugar output was decreased (figure 7) showing that these two substances vary independently of each other. This was apparent also during the pituitrin anti-diuretic test when the decrease in urinary output was accompanied by no comparable change in glycosuria.

of filtration through the glomeruli or not. When the filtration is augmented, e.g. by raising the pressure in the renal artery in the heart-lung-kidney preparation (deBoer and Verney) the amount of sugar in the urine is also increased; if the rate of filtration remains very constant, as is the rule normally, the sugar elimination like the urinary content of inorganic sulphate and creatinine is independent of variations in the volume of water excreted. Figure 3 (Exp. 3) illustrates this point." \*

In his experiments the calculated amount of reabsorbed glucose varied independently from the amount of urine or the amount of reabsorbed fluid or the height of the blood sugar. Our patient is, in some respects, similar to a partially phlorhizinized individual. During xylose clearance tests the tubular reabsorption of glucose (tables 2 and 4) seemed to vary in proportion to the percentage of glucose in the glomerular filtrate rather than in proportion to the absolute amount of glucose filtered. That is to say, less glucose was reabsorbed from the more dilute filtrate with the result that, probably by chance, the same amount of glucose reached the bladder urine in each period. Thus we see that tubular function of reabsorbing glucose does vary once the threshold level has been passed.† These changes point to control of the function of the tubular cells and the analogy to the anti-diuretic hormone is obvious.

### SUMMARY

We have reported observations on a patient with a very low renal threshold for glucose. It is apparent from our studies that water balance is an important factor in controlling the amount of sugar which appears in the urine in any 24 hour period although it has no effect on the total amount of sugar excreted over a long period of time. Sudden increase in fluid intake (forcing fluids) washes out large amounts of sugar and during

\* Poulsson's Figure 3:

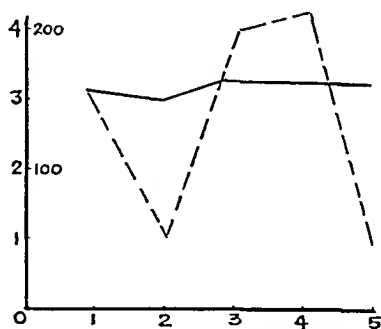


FIG. 3. Ordinate: -----c.c. of urine per hour.  
 —————g. glucose excreted per hour.  
 Abscissa: time in hours. (After Poulsson)

† In his book published October 1937, Homer Smith<sup>24</sup> reports unpublished experiments by Fisher and Shannon which, he says, demonstrate that in dogs once the threshold has been passed the kidneys maintain a constant rate of glucose reabsorption which is 200 mg. per minute and that all the filtered glucose in excess of this amount is excreted in the bladder urine. The protocols of these experiments are not presented, but the conditions of the acute experiment seem to be outside physiological limits ordinarily encountered.

periods of starvation, as after surgical operations, this leads to acidosis and should be avoided.

Certain data are needed to elucidate the kidney tubular activity which determines the renal threshold. The fact that the renal threshold varies during pregnancy, taken in conjunction with our observations, suggests hormonal control similar to that exerted by posterior pituitary extract on the renal tubules.

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## THE IMPORTANCE TO THE INTERNIST OF LATENT PARANASAL SINUSITIS \*

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PARANASAL sinusitis in its focal infective aspect has received considerable and merited attention in the last 15 years. The acute and chronic suppurative conditions, with pain, febrile course, frontals or antra opaque on transillumination, pus pouring from ethmoid-sphenoid region or copious purulent washings from an antrum, are easily recognized, and, in general, well handled.

Chronic hyperplastic sinusitis, on the other hand, is for the more part a milder condition whose usual manifestations are neither pronounced nor dramatic. The relationship of this lesion to asthma has been emphasized by Cooke.<sup>1</sup> We propose to discuss the part played by some of its milder forms in certain general disturbances and to call attention to the fact that its subjective local or rhinological manifestations may be slight or even nil; that diagnosis must be made by the internist; and that perseverance in treatment meets with a fair measure of success.

The predominance of general symptoms over local or head symptoms usually brings this case to the internist instead of the rhinologist, and because the objective findings and head symptoms are slight or do not trouble the patient at all, and because no suppurative condition can be demonstrated, some persuasion is ordinarily required to induce the specialist to display much interest.

The patient complains of aches and pains in varied regions of the body, and it is often impossible to determine whether these sensations have their origin in muscles, nerves or joints. Almost all complain of fatigue. A few show some slight temperature disturbance. Some are asthmatic. Chronic cough and morning clearing of the naso-pharynx are common. A considerable number have rather frequent colds, and we have come to feel that the incidence of two or more colds a winter is very suggestive of chronic sinus disease. The subjective symptoms of this group on the whole are general in nature and therefore they consult the general practitioner or the internist.

Examination shows congestion of nasal and pharyngeal mucous membranes; the turbinates may be swollen, or the septum deflected. The pharynx is solidly congested or shows a streaked appearance. It may be covered by a muco-purulent coating significant of discharge from posterior

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ethmoids and sphenoids. The tonsils if present are unhealthy, and the anterior pillars are injected.

This is the general picture of what may be termed "latent sinusitis," and the diagnosis of sinusitis should be made on the basis of such history and physical findings. Its more exact localization may be left to the roentgenologist and the rhinologist.

The real difficulties to be encountered arise at this point. If the patient is sent for roentgen-ray examination, the stumbling blocks are likely to be poor position in making the films and then poor interpretation. The films do not give good ethmoid or sphenoid exposures, or they are too hard, showing the bony structures, but not the soft tissues. Again one often receives negative interpretations of what are obviously positive findings, so that we are in the habit of interpreting films for ourselves, insisting always on seeing them, and never accepting a mere written or verbal report.

The next difficulty apt to arise is with the rhinologist. A case which does not reveal pus pouring from some of the posterior group of sinuses, or frank purulent discharge on washing an antrum, is regarded as having no demonstrable sinus disease, and word comes back that there is nothing for the specialist to do. Or if he does find ethmoid or sphenoid disease he tells the patient that nothing worth while can be done about it and he had better save his money.

TABLE I

Subjective Symptoms in 100 Consecutive Cases of Antrum Infection  
Suppurative type 51  
Hyperplastic type 49

General		Local	
Lassitude.....	82	Discharge.....	77
Repeated colds.....	63	Pain (head).....	61
Rheumatic pains.....	50	Obstruction.....	11
Cough.....	36	No local subjective symptoms.....	16
Indigestion.....	33		
Loss of weight.....	23		
Asthma.....	14		
Hay fever.....	8		

*Of this last group of 16*

Suppurative type.....	5
Hyperplastic type.....	11

\* \* \* \* \*

Table 1 shows the typical subjective symptoms and their relative incidence in 100 consecutive cases with antrum infection, both suppurative and hyperplastic. This particular sinus (the antrum) was selected for study and discussion because of its easy demonstrability by transillumination and by roentgen-ray, and because the use of lipiodol serves to give a graphic idea of the degree of thickness of the mucous membrane and the change which occurs in it under treatment. It is to be understood, however, that all that we say here regarding antral infection applies with equal force to ethmoid and sphenoid cases.

The striking thing in this table is that 16 of the entire group, 11 of which were hyperplastic cases, had no subjective symptoms referable to the

nose and throat, and that all of them consulted the internist first, on account of generalized symptoms such as lassitude, rheumatic aches and pains, indigestion, etc. Local treatment by the rhinologist was the chief, if not the sole, measure employed in treatment and resulted in relief of symptoms in each case.

Four typical cases have been selected from the hyperplastic group of 11 and are reported herewith.

#### CASE REPORTS

*Case 1.* Complains of lassitude for two years, lumbar pain the past eight months and 15 lbs. loss of weight in six months. There are no subjective complaints referable to the nose and throat.

Roentgen-ray shows a moderately cloudy right antrum. Washings from the antrum are grossly clear, centrifuged and examined microscopically; there are many epithelial cells with cast off cilia. No leukocytes.

Culture: two colonies *Staphylococcus albus*.

Lipiodol injected into the antrum shows a tremendous thickening of the mucous membrane. Blood: slight polymorphonuclear leukocytosis.

Treatment over a period of two months consisted of three irrigations of the antrum, three lipiodol instillations, and five argyrol or cocaine packs. At the end of two months' treatment the lipiodol injection of the antrum showed a mucous membrane of normal thickness. Follow up (four months after treatment was begun): No pain for two months; no fatigue for three months; gain eight pounds in weight (figure 1).

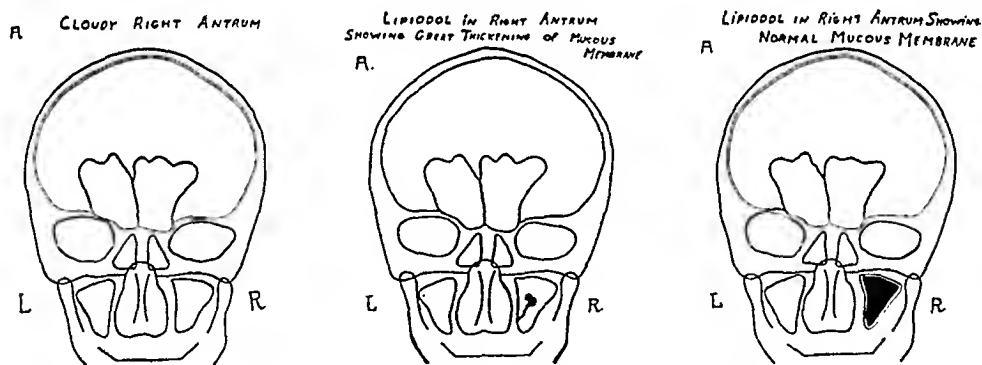


FIG. 1. Diagrammatic illustration of Case 1, before treatment and after six months treatment.

The lipiodol shadows are drawn as nearly as possible to the outlines of the roentgen-ray shadows.

The diagrammatic scheme is employed in preference to photographs of the actual films because of its simplicity and to avoid the lack of detail and consequent confusion which the photograph of the film involves.

*Case 2.* Complains of marked lassitude the past six years and frequent colds the past four years. No local subjective symptoms.

Roentgen-ray reveals a hazy left antrum, and lipiodol injection shows a very distinct thickening of the mucous membrane. Washings from the left antrum clear, microscopic examination of the centrifuged specimen showed no cells, and culture was sterile. Blood showed a slight polymorphonuclear leukocytosis. Treatment was over a period of five months and consisted of six irrigations of the left antrum, one lipiodol instillation, and 12 argyrol or cocain packs. Roentgen-ray with lipiodol toward the

end of that period showed normal mucous membranes. Three years later: there had been no fatigue in that time, and very few colds. (Figure 2.)

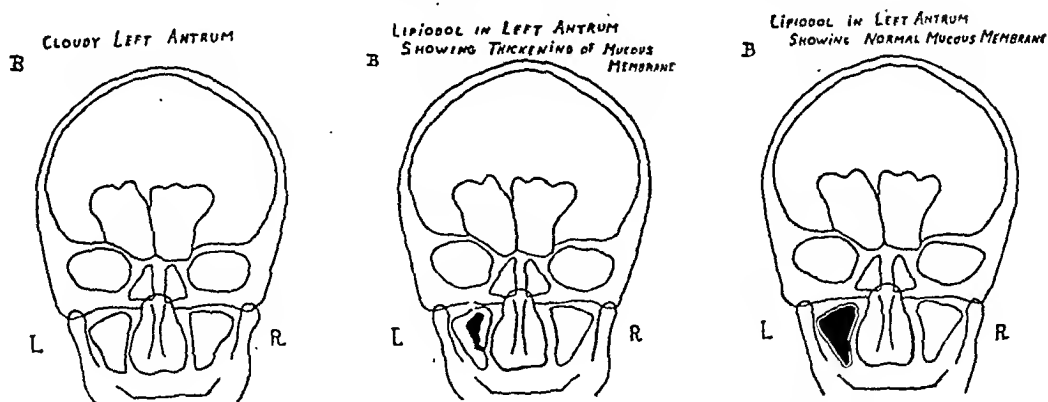


FIG. 2. Diagrammatic illustration of Case 2, before treatment and after five months treatment.

*Case 3.* This patient had experienced abnormal fatigue for five years, and for past two months was troubled with pain in the right hand and in the lumbar muscles. A cloudy left antrum was shown on roentgen-ray, which filled very poorly with lipiodol, showing a mucous membrane almost a quarter of an inch in thickness. Washings from the left antrum were clear. Microscopic examination: A few leukocytes and ciliated epithelial cells. Culture sterile. Blood: Polymorphonuclear cells very immature—pronounced shift to the left. Treatment over a period of two months consisted of six irrigations and two lipiodol instillations. At the end of this time lipiodol roentgen-ray film showed a mucous membrane of normal thickness. The patient was completely relieved of fatigue and pain and was still without symptoms two years later. (Figure 3.)

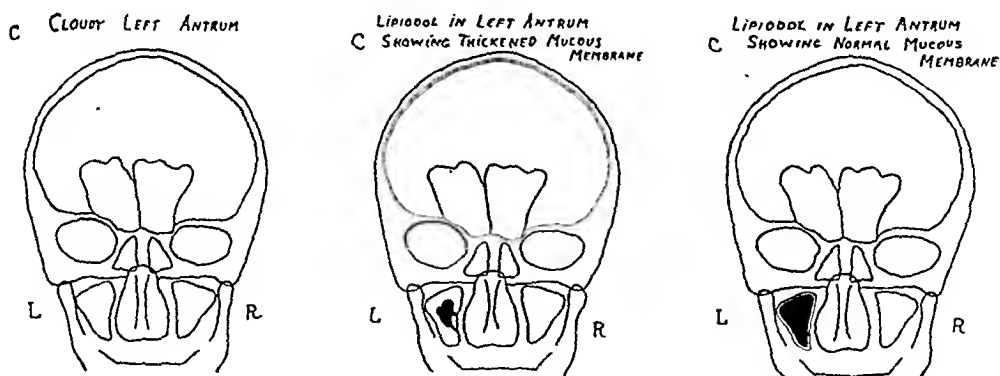


FIG. 3. Diagrammatic illustration of Case 3, before treatment and after two months treatment.

*Case 4.* This patient complained of sciatic pain and dry cough for the past four months. He had suffered undue fatigue for five months.

The left antrum and left anterior ethmoids were cloudy on roentgen-ray and with lipiodol the antral mucous membrane was shown to be between  $\frac{1}{8}$  and  $\frac{1}{4}$  inch in thickness. Washings were clear: centrifuged and examined microscopically showed fragments of epithelium, ciliated cells and cholesterol crystals. Blood showed a large percentage of immature neutrophilic leukocytes. Treatment over a period of two months comprised two irrigations of the left antrum, two lipiodol instillations, one ephedrine displacement, and six argyrol or cocain packs.

Roentgen-ray with lipiodol at the end of that period showed a mucous membrane of normal thickness. Follow up six months after treatment was begun: no pain or cough and no fatigue. (Figure 4.)

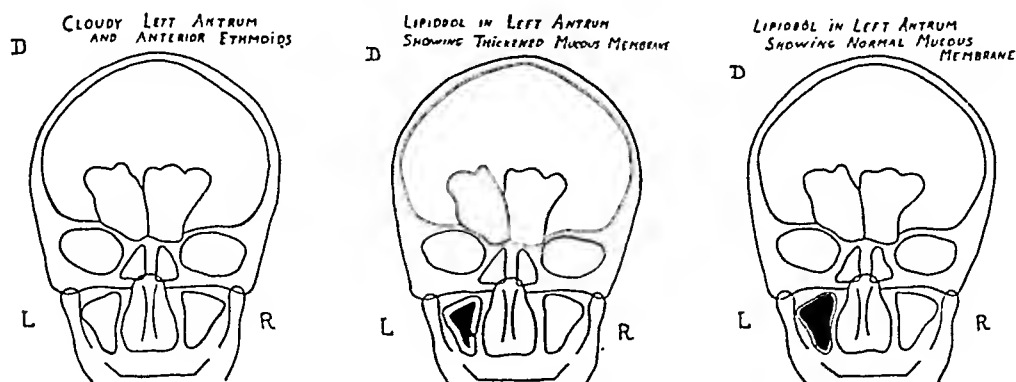


FIG. 4. Diagrammatic illustration of Case 4, before treatment and after two months treatment.

### DISCUSSION

It will be noted: First, that the complaints of these patients are of lassitude, and lumbar or sciatic pain. One had frequent colds, but not one complained of obstructed breathing, excessive nasal secretion, or head pain.

Second, antral cloudiness and a considerably thickened mucous membrane on lipiodol injection were demonstrated by roentgen-ray.

Third, washings from the antrum in all cases were grossly clear and in three cases sterile on culture, while in Case 1 two colonies of *Staphylococcus albus* were grown, which were probably contaminations.

Fourth, that conservative treatment over a period of two months in three cases, five months in the fourth, resulted in shrinkage of the antral mucosa to a normal thickness, and great if not complete relief of fatigue and rheumatic symptoms. A gain of 8 lbs. weight resulted in one case (Case 1) and freedom from colds in another (Case 2). The follow up data extended over periods ranging from six months to three years.

An important question arises here. If the washings from these antra were sterile, what was the pathology and the origin of symptoms in these cases?

We believe that there is a direct analogy between infection in this locality and that in the gall-bladder. It has been recognized for some years that the important locus of gall-bladder infection is not on the surface of the gall-bladder mucous membrane, but in the submucosa itself.<sup>2</sup>

The same thing has been reported by R. A. Cooke<sup>1</sup> in regard to antrum infection, and we have verified this by taking the mucosa excised at radical antrum operations (Caldwell-Luc method), sterilizing the outside with iodine and alcohol, grinding up the mucosal segment and growing pure cultures of bacteria therefrom.\* It seems probable that in the chronic cases

\* It is to be noted that, in the cases whose tissues were thus examined, surface cultures made prior to operation were sterile, as were the surface cultures made at the time when the membrane was removed at operation.

the bacteria have become well imbedded in the body of the mucous membrane, where they may lie for some time dormant as far as any surface expression of their presence is concerned (that is, secretion), but elaborating toxins, which, getting into the blood stream, produce symptoms in distant parts of the body.

This is the type we term "latent" sinusitis, and all that has been said above applies with equal force to the infections of the ethmoid and sphenoid cells. The later, however, are not so accessible to roentgen-ray demonstration as the antra, because it is difficult to retain lipiodol in them for the making of films, and therefore we have confined our demonstration to antrum infections. It must be emphasized too that conservative treatment of the posterior group of cells, directed toward improving drainage by shrinking down the nasal tissue, is quite as satisfactory as in the cases described.

The importance of the whole subject lies in this: The diagnosis must often be made by the internist, whom these patients as a rule consult before anyone else; or they come to him having been told by the rhinologist there is nothing to be done, or that he has done all he can. Having convinced himself of the diagnosis the internist must insist on treatment being instituted and carried on for a sufficient length of time. It requires patience and persistence, but has its reward, and quite frequently results in relieving symptoms which have been bothersome and crippling for months or even years.

### CONCLUSIONS

There may therefore be an infected mucous membrane which produces little or no discharge for varying periods of time, but is, nevertheless, quite capable of causing focal or generalized symptoms. Evidence of such a condition may be obtained from the patient's history, the presence of congestion or swelling of the nasal mucosa, and departure from the normal on roentgenological examination, which must be accurately made and carefully interpreted. The presence of such infection once established, prolonged treatment and patient handling must follow to insure results. Radical procedures are rarely needed in the class of case here presented.

### SUMMARY

1. A type of infection of the paranasal sinuses is discussed in which the pathology consists of a hyperplastic inflammation with the bacteria imbedded in the submucosa *without* surface discharge, but with a greatly thickened mucous membrane, as demonstrated by roentgen-ray with lipiodol injection.

2. The patient's complaints are largely of a general type and very little directly referable to the nasal passages.

3. A table is offered showing the incidence of symptoms, general and local, in 100 consecutive cases of antrum infection of both suppurative and

hyperplastic types, and it is emphasized that of the entire group 16 per cent had no local subjective symptoms whatever.

4. Four of these cases are reported, demonstrating: (*a*) absence of local subjective symptoms; (*b*) positive roentgen-ray findings with lipiodol; (*c*) negative antrum washings; and (*d*) improvement under treatment.

5. It is important that diagnosis of this type of case should be made by the internist, on the basis of history, presence of local signs and abnormal findings on roentgen-ray.

6. Sphenoid and ethmoid infections exhibit the same characteristics as the antral cases, the latter being employed for this study because of their greater ease of demonstration by transillumination, roentgen-ray, etc.

7. Prolonged and careful treatment is essential, and radical procedures are seldom required.

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## ACUTE INSUFFICIENCY OF THE ADRENAL GLANDS; REPORT OF 2 CASES \*

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THE syndrome of chronic adrenal insufficiency has received considerable attention in the literature in the past decade due to increased knowledge of the pathologic physiology and improvement in therapeutic methods.<sup>1, 2, 3</sup> Acute failure of adrenal function, beyond those cases noted in the newborn as a result of trauma or hemorrhagic disease, is an uncommon finding.

Reports of cases of acute insufficiency of the adrenal glands have appeared in the literature. The earliest such case noted is Case 10 in the original paper of Addison.<sup>4</sup> This case is not so typical as many of the other subsequent reports. Addison's case was in a 28-year-old female with cancer of the uterus who died four days after admission. At necropsy she showed pigmentation of the skin. "Although the right adrenal was intact, the left had a malignant tubercle which had developed at that precise point where the large vein escapes from the organ; this tubercle projected into the interior of the vein, so as almost or entirely to obstruct it, and had, moreover, led to rupture and effusion into the capsule itself." This case of advanced malignant disease came to an acute termination with a sudden hemorrhage into the gland secondary to a metastatic focus occluding the vein. The apparently intact right adrenal was incapable of supporting life.

Since then there have been sporadic reports of cases of this type. Lavenson<sup>5</sup> in 1908 reported one such case due to thrombosis of the suprarenal veins with hemorrhagic necrosis of both capsules. Lavenson felt that the degree of tissue destruction was in no way a measure of functional incapacity but when such destruction reached a certain degree, or involved certain elements, clinical signs were manifested.

Boyd<sup>6</sup> describes a 38-year-old soldier who had been quite active. He was found unconscious in his room and was taken to the hospital where he died two and one-half hours after admission. Autopsy revealed old fibrotic tuberculosis of the apices of both lungs with a cavity the size of a hazel nut at the right apex. There was complete obliteration of both pleural cavities by firm adhesions. Except for small islands of cortical tissue in the left adrenal there was complete replacement of both adrenal glands by structureless amorphous acidophilic tissue which showed caseation necrosis, numerous endothelial cells and giant cells. No recognizable medullary tissue was present.

Several other reports are found in the literature of relatively sudden

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death after minor illnesses, trauma or operative procedure in which on autopsy extensive tuberculous disease of the adrenals was found. Oudard<sup>7</sup> reported a case of a male, aged 42, who developed mild asthenia following an accident. After an operation for non-union, he went into coma and died. The adrenals were completely replaced by large confluent tubercles. Terzani<sup>8</sup> observed a young male adult who after a three-day influenza-like illness at home was admitted in coma. His previous history was irrelevant in all respects. After admission he became violent, incoherent and incontinent. There was slight pigmentation of the skin with pigmented areas of the palate, penis and scrotum. Death took place in 24 hours. Section showed bilateral caseation of the adrenals, the peripancreatic and periaortic nodes. The apex of the left lung showed a fibrotic lesion surrounded by a few areas of caseous pneumonitis. Cohoe<sup>9</sup> reported a case in which death occurred in five days following vascular changes in the adrenals.

#### CASE REPORTS

*Case 1.* J. McD., aged 41, male, married salesman, admitted in coma April 5, 1935, 4:50 p.m. and died four and a half hours later. History was obtained from wife. His father died of malignant disease of the throat, his mother was living and well. There were no siblings. The previous history revealed pleurisy, emphysema, pneumonia and measles. The time relationship of these illnesses was unknown. At the age of eight he had right hip disease. This joint became stiff and for the past eight years there was a discharging sinus over this joint. Last year he had "neuritis" of his shoulders and arms. He had been married for 15 years. There were two children living and well. In 1923 his wife had a spontaneous miscarriage. The deceased had always been a heavy smoker and was a heavy drinker at intervals. For an indefinite period he had been losing weight, tiring easily and showing some darkening of the skin. He remained at his work, never losing any time.

On the day prior to his admission he drank heavily but was able to drive his car home. His wife did not hear him enter. In the morning he could not be aroused. Respiration was stertorous. On the advice of the family physician the patient was hospitalized that afternoon. On admission the patient was in coma and could not be aroused. Breathing was noisy and irregular. There was evidence of loss of weight. The skin showed scattered areas of brownish pigmentation more marked over the scrotum. The pupils were equal and reacted to light. The nose and ears were negative. The lips were cyanotic. The throat could not be visualized because of inability of patient to cooperate in opening his mouth. There was no neck rigidity. No peripheral lymph nodes were palpable. The chest showed good resonance. Coarse moist râles were present throughout. The heart sounds were regular, but the details were masked by the noisy respiration. The abdomen was held rigidly. No viscera or masses were palpable. The right lower extremity was smaller and shorter than its fellow. There was a draining sinus tract on the anterior aspect of the right hip. There was no edema.

Course: On admission the temperature was 101.6° F.; pulse 94, respirations 20. Blood pressure 110 systolic, 80 diastolic. Hemoglobin 82 per cent. Red blood cells 4,600,000; white blood cells 10,400. Polymorphonuclear leukocytes 66 per cent. Lymphocytes 34 per cent. Urine: albumin: trace; sugar: negative; acetone: one plus. Blood chemistry: urea: 16.7 mg. per 100 c.c.; creatinine: 1.43 mg. per 100 c.c.; glucose: 62.0 mg. per 100 c.c. Wassermann reaction negative. Coma deepened rapidly and patient died 4½ hours after admission.

## AUTOPSY FINDINGS

Section performed 13½ hours after death. The right lower extremity was four inches shorter than its fellow. There was marked decrease in circumference at all levels. The limb had a shriveled, wasted appearance. Just below the lateral end of

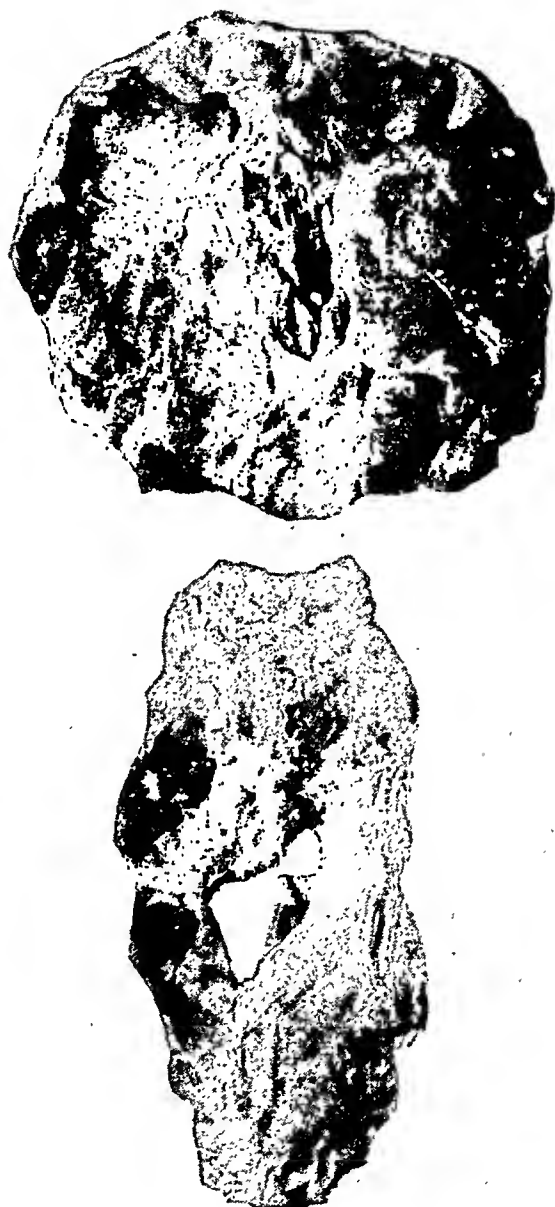


FIG. 1. Gross appearance of adrenals. The right adrenal, above, has been split laterally; the left, below, in a horizontal plane.

the inguinal ligament there was a two-inch vertical scar. The proximal part of this was separated, red in color and covered by inspissated pus. There were 10 old depressed stellate scars scattered about the anterior lateral and posterior aspects of the hip region. The skin of the ventral surface of the body was darker than the dorsal

surface. This pigmentation was more marked about the scrotum. A triangular patch of pigmentation was noted on the left side of the buccal mucosa. The scalp hair was abundant but gray-streaked. The left supraclavicular fossa was deeply retracted. The trachea was slightly deviated to the right.

Examination of the thorax showed a smooth right pleura except for a line of firm adhesions binding visceral and parietal layers. This line exactly followed the interlobar fissure separating the right upper from the middle lobe. The left pleural cavity was completely obliterated. Every part of this lung was so intimately adherent to the thorax that the lung was removed from the chest with considerable difficulty. The lungs were intensely congested and edematous. There was no scarring of the apices or cavitation. At the apex of the left lower lobe just beneath the pleura was a small,



FIG. 2. Low power ( $\times 200$ ) showing island of cortical cells.

hard, encapsulated nodule measuring 1 by 0.5 by 0.5 cm. On section there was a hard cortex with a soft, cheesy, white center (Kuss-Ghon primary complex).<sup>10</sup> There was a moderate dilatation of the bronchi and bronchioles of the left lower lobe. The trachea and peribronchial lymph nodes were enlarged, firm and on section were gray with mottled black central areas.

The pericardial sac was completely obliterated by dense firm adhesions. The left pleura was adherent to the pericardium. Over the anterior aspect of the heart at the base there was one area about one and a half cm. in diameter which was bony in consistency. The heart weighed 270 grams (in spite of the adhesive pericarditis, the underlying lesion resulted in a small heart). The chambers, valves and valve orifices

were average. There was a minimal degree of atheromatosis of the coronary arteries and of the aorta.

The abdominal viscera were in average relationship. No fluid was present in the cavity. The gross appearance of the liver, spleen, pancreas, kidneys, bladder and prostate was not noteworthy. The gastrointestinal tract showed no ulcerations or scarring. There were a few caseous and calcified nodes of various sizes at the root of the mesentery.

The adrenal glands were appreciably larger than usual. The left measured 4 by 3 by 2 cm.; the right 4 by 4 by 2 cm. Both capsules were firm and nodular. The cut surface was grayish white in color with many irregular soft caseous areas. Throughout both glands there were occasional islands of chrome yellow tissue.

Head: No trauma of the scalp. The vault and base of the skull were intact. The accessory nasal sinuses, middle ear and mastoid were normal in appearance. There was moderate edema of the brain. Section after fixation showed no noteworthy variations. The venous sinuses of the dura were smooth walled throughout.

Histologic sections of the skin show dopa-positive cells in the corium. The adrenal glands were almost completely replaced by large confluent areas of caseation necrosis with frequent Langhans' giant cells. There were scattered foci of recognizable cortical cells. These showed vacuolated cytoplasm. The primary pulmonary complex showed a well encapsulated caseous area surrounded by a zone of lymphocytes. There were several areas of fibrosis in the right upper lobe.

A purulent bronchitis was present in the left lower lobe. Moderate cloudy swelling and granular degeneration were present in the hepatic cells. There were several scattered areas throughout the liver consisting of endothelial cells and lymphocytes surrounding a small necrotic center. These tubercles were all of approximately equal size. The spleen, kidneys, prostate and bladder showed no significant abnormalities. The aorta showed minimal intimal atheromata. The base of the heart showed calcification beneath the adherent pericardium. No amyloid changes were present in any organ.

*Anatomical Diagnosis:* Tuberculosis of the adrenals; primary infective complex, in apex of left lower lobe; caseous tuberculosis. Tracheal and peribronchial tuberculous lymphadenitis; mesenteric tuberculous lymphadenitis; miliary tuberculosis of the liver. Tuberculosis of the right hip joint; obliterative pleuritis (left); obliterative pericarditis; calcification of the pericardium.

*Case 2.* M. N., aged 21, single, had no complaint until 48 hours before admission when he went to bed complaining of an aching feeling in lower extremities, but his mother stated that he frequently had the same complaint because of his occupation as a shipping clerk. On February 2, 1938, he awoke and complained of a headache and generalized pains over his body. He went to work but had to return home because of a severe headache and a feeling of weakness. On arriving at home he vomited. The vomitus did not contain blood. That evening he vomited twice. The following morning, February 4, 1938, he arose and still complained of headache, and in addition his mother noticed that his speech was thick and difficult to understand. Patient became irritable, wanted to be left alone and then would demand things in a very irritable tone of voice. He responded to questions only after his mother would scold him and then in a thick voice which was difficult to understand. He did not vomit any more but felt nauseated. A physician was called and found that he had a temperature of 106° F. and advised hospitalization. He was admitted on February 4, 1938, at 8:04 p.m. in a semicomatose state, irrational and uncoöperative; extremities were cold and clammy. Respirations were normal and the temperature was 105.2° F. The only positive findings were rigidity of the neck, tachycardia, no blood pressure obtainable, pulse imperceptible, extremities cold and knee jerks were absent. No other neurological signs were present.

A spinal tap was performed—15 c.c. of clear fluid obtained—under a pressure of

16 mm. of mercury. There was a positive Queckenstedt. About one-half hour after tap the respiration became irregular and five minutes later, stopped entirely. The heart sounds were heard for a few minutes and then were no longer heard. The patient expired at 10:08 p.m., two hours and four minutes after admission. The blood chemistry was as follows: N. P. N.: 91.0; urea N 52.0; creatinine: 2.2; glucose: 107.0; urea ratio: 56.0. Urine: specific gravity: 1.009; albumin: 2 plus; leukocytes: 20-25 per high power field and numerous finely granular casts.

#### AUTOPSY FINDINGS

Section performed 10 hours after death. The body was that of a young adult male, 5 feet 10 inches in height and well developed and muscular. There was a moderate diffuse dependent hypostasis. There were no evidences of external injury.

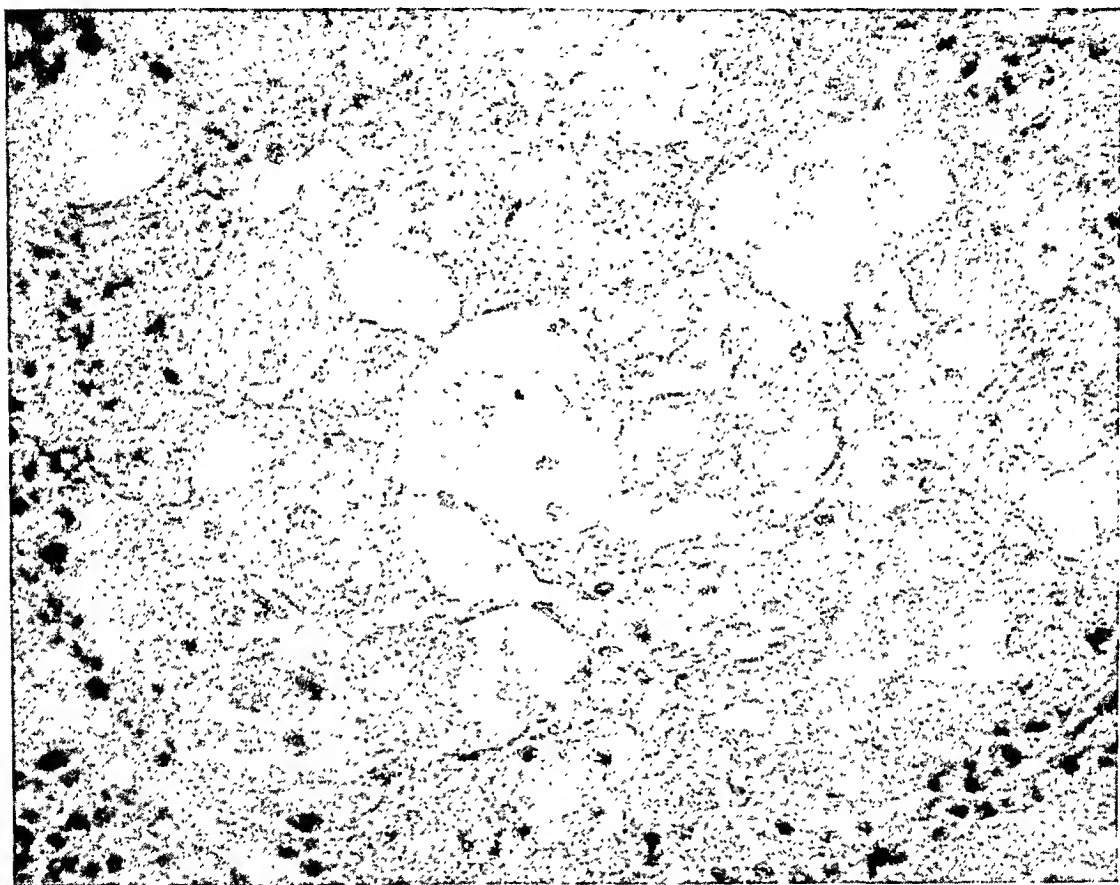


FIG. 3. Illustrating hydropic changes in cortical cells.

There were no scars. The hair of the scalp was brown and abundant. The pupils were markedly dilated and irregular. There were marked subconjunctival hemorrhages of both eyes. There were no palpable lymph nodes noted. There was no peripheral edema, nor were the fingers clubbed.

There was no free fluid in any of the serous cavities. Examination of thorax showed voluminous lungs which were deep mahogany brown in color with interspersed purplish areas. On section bloody frothy fluid was expressed from all surfaces. There were no areas of consolidation. The trachea and bronchi were filled with pink frothy fluid. The mucosa of the bronchial tree was smooth throughout. The

branches of the pulmonary artery within the lung parenchyma were smooth walled. On search, no primary infective nodule could be demonstrated. There were no significantly enlarged tracheal or peritracheal or mediastinal lymph nodes. The heart, which weighed 370 grams, showed numerous subepicardial hemorrhages. The valves were smooth, translucent and showed average appearances throughout. There were no changes in the myocardium. The aorta was normal in circumference and smooth walled. The coronary vessels were smooth walled throughout. Both superior and inferior venae cavae showed no evidence of thrombosis. The liver was smooth walled and glistening, was deep mahogany brown in color and on section showed a diffuse nutmeg appearance. The biliary system was normal throughout. The pancreas was normal in appearance. The spleen showed no abnormalities. The gastrointestinal tract was smooth walled throughout and showed no scars or tumors. The kidneys combined weighed 280 grams and were flabby in consistency. The capsule stripped with ease. There were numerous small surface hemorrhages. On section the cortex was clearly demarcated from the medulla and of average width. There were no hemorrhages on section. The pelves were smooth walled. The ureters and bladder were normal in appearance.

The adrenals were embedded in a large amount of fat tissue and felt solid on palpation. The right adrenal was divided into two roughly equal halves by firm scar tissue, one portion measuring 3.5 by 2 by 1 cm., the other 2.5 by 1.5 by 1 cm. On section the cut surface was homogeneously yellow in color and resistant. There was an irregular zone of hemorrhage peripherally, in both portions. There was no grossly recognizable adrenal tissue. The left adrenal was irregularly oval in outline measuring 4 by 3 by 2 cm., firm in consistency and resistant to section. The cut surface was homogeneously yellowish white in color.

Head: There were no scars or hematomas of the scalp. On removal of the calvarium, no fractures of the vault or base of the skull were found. The brain was markedly congested, but no exudate or hemorrhage was present. Section of the brain after fixation showed no areas of hemorrhage or tumefaction. The ventricular system was normal. The pituitary was average in size.

Microscopic: Histologic sections of the adrenals showed extensive caseation throughout, surrounded by irregular zones of lymphocytes with irregular endothelioid cells and with not infrequent Langhans' giant cells. Sections from the left adrenal showed no recognizable cortical or medullary tissue. There was a focal lymphocytic infiltration in the surrounding fat. The right adrenal showed several irregular areas of recognizable cortical tissue, the superficial layers of which showed pyknotic nuclei. The cytoplasmic outlines were obscured. In the deeper layers there was marked cloudy swelling and granular degeneration of these cortical cells. Irregular lymphocytic infiltration was present in this cortical tissue.

Sections from other organs showed no significant changes. There was no evidence of tubercle formation in any of the other viscera.

*Anatomical Diagnosis:* Bilateral tuberculosis of the adrenal glands.

#### COMMENT

The first case presented showed extensive obliteration of the suprarenal capsules by a caseating process associated with a childhood form of tuberculosis, with tuberculosis of the right hip joint. There were several remnants of cortical tissue scattered through the caseous areas. These islands of cortical tissue were apparently sufficient to enable him to keep at his daily work as a salesman. It was not until a heavy drinking episode took place that acute failure ensued. There was some functional incapacity as shown by skin pigmentation, loss of weight, fatigability and asthenia.

In the case reported by Terzani<sup>8</sup> the precipitating factor was an upper respiratory infection. Here too, an almost completely obliterated pair of adrenal glands were able to carry on life, but an additional load, here an acute infection, "broke the camel's back."

In this connection the observation of Sezary<sup>11</sup> is of note. He states that 90 per cent of the adrenals can be destroyed without fatal issue, or without apparent clinical signs. To be sure, the functional capacity of such a gland has little or no reserve and any undue, unusual or increased demand is met with a sudden collapse. Boyd<sup>6</sup> states that similar cases of acute insufficiency are seen with anatomically intact adrenals but with degeneration of other chromophil tissue and abdominal sympathetic ganglia. It is noteworthy in this connection that in tuberculosis sanatoria, tuberculous disease of the adrenals is not infrequently discovered at autopsy. These cases have no clinical evidence of Addison's syndrome. The histologic picture of the glands shows varying amounts of cortical tissue. Lavenson<sup>5</sup> has described four clinical types of acute insufficiency of the adrenals: an acute abdominal form with vomiting and shock; a cerebral form with convulsions and coma; an asthenic form; and lastly a form with sudden death without premonitory warning. Both of our cases belonged to the cerebral type. It will be remembered that in the first instance the acute adrenal insufficiency followed a drinking bout. Chemical examination of the brain, however, revealed only a slight trace of ethyl alcohol.

Such cases as these have a medico-legal bearing. The importance of sudden death from such a progressive lesion must be considered. The first case at hand was considered as an alcoholic death until autopsy and chemical analysis were done; the second was thought to be due to meningitis.

### SUMMARY

Two cases of relatively sudden death are reported due to extensive tuberculous disease of the adrenal glands.

The cases reviewed in literature, as well as our two cases, have all shown devastating lesions in the glands with but small strands of cortical tissue. These glands were capable of carrying on until an extra functional load was experienced.

The possibility of acute insufficiency of the adrenal glands should be considered in medico-legal cases.

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# STUDIES OF IRON METABOLISM IN A CASE OF HEMOCHROMATOSIS \*

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IN connection with the clinical study and care of patients with hemochromatosis seen in this clinic,<sup>1</sup> it seemed desirable to investigate the iron metabolism by means of balance studies. This was thought particularly worthwhile because of the paucity of such data in the literature. Only four reports have come to our attention, namely those of Howard and Stevens,<sup>2</sup> McClure,<sup>3</sup> Dry<sup>4</sup> and Fowler and Barer.<sup>5</sup>

## CASE REPORT

Mr. F. H. was first seen on August 2, 1933 when 47.6 years of age. Sugar had been found in his urine first in August 1931 and from his history it was estimated that the onset of the diabetes had been in January of that year. The symptoms at onset had been polyuria, polydipsia, polyphagia, and loss of weight and strength. The bronze color of his skin had been noted first in November 1931, and while under the care of the Lahey Clinic in January 1932, the diagnosis of hemochromatosis had been made and verified by a biopsy of skin (examined by Dr. Shields Warren, Pathologist to the New England Deaconess Hospital).

*Family History.* The patient's mother, who was 78 years old in 1933, was said to have had diabetes for 10 years. A letter from her family physician in 1936 indicated that she occasionally had glycosuria following dietary indiscretions but that otherwise the urine was sugar free. It may, therefore, be regarded as doubtful whether the mother really has true diabetes. The patient's sister, who in 1933 was 44 years old, has sugar in the urine at times, but a sucrose tolerance test was normal in 1933. A maternal uncle of the patient is said to have died from diabetes. The patient's father died of nephritis at the age of 77. The patient has no brothers and has one sister other than the one mentioned above; this second sister is living and well and in 1933 was 42 years old. The patient's wife is living and well. There is one child living and well who in 1933 was 23 years old. No relative of the patient has been known to exhibit signs or symptoms suggesting hemochromatosis.

*Past History.* Past illnesses included measles, mumps, and whooping cough in childhood and appendicitis at the age of 18 years. For years the patient had been troubled by chronic catarrh. Before prohibition he had drunk much beer for years, three or four bottles a day, but very little other liquor. Since prohibition he had had no beer but had had occasional whiskey highballs although never to excess. He had had practically no liquor since 1931.

*Physical Examination.* Physical examination during his first hospital admission showed the heart to be normal in size and regular in rhythm; a systolic murmur could be heard over the whole precordium. The lungs were clear. The abdomen was soft and non-tender although the spleen could be touched and the liver could be felt to descend on inspiration to the level of the umbilicus; it was hard in consistency. Pulsations could be felt in the dorsalis pedis arteries in the feet, and the patellar reflexes were equal and normally active. The blood pressure was 110 systolic, 70

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diastolic. There was slight pitting edema over the shins. Sclerosis of the radial arteries was graded as 3 on a scale of 4. The skin over the whole body had a queer brownish hue as if dirty; the arms and legs over the regions which had been exposed to the sun showed particularly the characteristic bronze color. The hair over the head and the axillary and pubic hair was scant. There was atrophy of both testes. (The patient stated that there had been a loss of sexual power and desire for three or four years.)

*Laboratory Findings.* The admission specimen of urine contained 10.8 per cent sugar and gave a 1+ reaction with ferric chloride. The specific gravity of the urine was 1.045, the reaction was acid, there was a very slight trace of albumin, and no bile. In the sediment there were no casts and an occasional red blood corpuscle and an occasional white blood cell per high power field of the microscope. The red blood count was 4,870,000, hemoglobin (Newcomber) 80 per cent, and white blood count 9,350 to 11,550. Examination of a stained smear showed no abnormalities. The blood non-protein nitrogen varied from 27 to 33 milligrams per 100 c.c. of blood. The blood cholesterol was 200 milligrams per cent. During a two-week stay in the hospital the fasting blood sugar varied from 0.18 per cent to 0.27 per cent. The blood bilirubin was normal, 0.2 milligram per 100 c.c. (monophasic reaction). The basal metabolic rate was plus 7 per cent. The blood serum protein was 6.0 per cent. A fragility test of the red blood corpuscles showed hemolysis to begin at a concentration of salt of 0.42 per cent and to be complete at 0.32 per cent. Urobilinogen in the urine was positive on two occasions in a dilution of 1:20, once in a dilution of 1:30, twice 1:50, and once 1:100. The bromsulfalein test of liver function showed no retention of the dye in the blood after 30 minutes. The blood calcium was 10.4 milligrams per 100 c.c. A roentgenogram of the chest on October 31, 1935 revealed nothing abnormal.

*Course in Hospital.* During this first two-week stay in the hospital in 1933 the patient's diabetes was gradually brought under control, and at the time of discharge his urine had been essentially free from sugar for five days on a diet of carbohydrate 201, protein 79, and fat 48 grams, 1552 calories per day and on 16 units of insulin before breakfast, 8 before lunch, 12 before supper, and 2 at bedtime.

*Subsequent Course.* The patient has been seen at fairly frequent intervals since the first admission both in the office and during hospital stays. The hospital admissions other than the first one were as follows: October 28 to November 2, 1935, October 25 to November 25, 1936, and October 3 to 9, 1937. There has not been a great deal of change in his condition during this time and in general he has held his own. The body weight without clothing at the end of the first admission was 119½ pounds (54.3 kg.) and at the end of the admission of October 1937 was 114 pounds (51.8 kg.). His health has been fairly good although his endurance and strength are by no means normal. The color of the skin has remained about the same. In October 1936 he was shifted to protamine zinc insulin and at the present time (January 1938) \* his diabetes is under good control on 36 to 40 units of protamine zinc insulin once daily in the morning before breakfast. His present diet (so arranged in an attempt to maintain body weight) is carbohydrate 206, protein 73, and fat 116 grams, 2,260 calories daily. Examination of a single specimen of urine in October 1937 showed a specific gravity ranging from 1.010 to 1.020, a negligible amount of albumin, no bile, and in the sediment no blood, pus, or casts. A test for urobilinogen in the urine was positive in 1:30 dilution. The blood pressure was 128 systolic and 80 diastolic. A bromsulfalein test of liver function showed no retention of the dye at

\* Note added March 22, 1939. The patient's condition has changed very little during the past year. His diabetic condition is kept under good control with 8 to 10 units of unmodified insulin and 40 units of protamine zinc insulin taken in the morning before breakfast. The liver is huge, the lower margin being felt upon inspiration at the level of the iliac crest. The spleen can be felt with the patient in the right lateral position.

the end of 30 minutes. A red blood count on October 9, 1937 was 4,320,000 and white blood count 9,600, hemoglobin 75 per cent, and the smear normal. The size of the liver and spleen has remained about the same. The liver descends 9 cm. in the mammary line and crosses the abdomen at the level of the umbilicus. The spleen can just be touched with the patient in the right lateral position. A rectal examination reveals large external hemorrhoidal tags.



FIG. 1. Low power view of section of skin removed from Mr. F. H. Note the heavy deposit of melanin in the cells of the basal layer of the epidermis. Part, though not all, of the pigmentation in the rest of the section is due to deposits of iron-containing pigment. (Potassium ferrocyanide, counterstain 0.5 per cent basic fuchsin;  $\times 48$ )

Laboratory data of a general nature which were collected in the hospital admission of October 25 to November 25, 1936 during which the studies of iron metabolism were carried out, are summarized herewith. The fasting blood sugar varied from 0.05 per cent (low because of an excessive dose of protamine zinc insulin) to 0.26 per cent. The blood non-protein nitrogen on one occasion was 27 and on another, 29 milligrams per 100 c.c. The urine contained little or no albumin and in the sediment there were no pus, blood or casts. The number of white blood cells varied from 6,200 to 10,150 per cu. mm. A tabulation of five differential counts on different days scattered through the month showed the percentage of neutrophilic leukocytes to average 49 and of lymphocytes, 44; otherwise the stained blood smear was not remarkable. A

phenolsulphonephthalein test of kidney function showed an excretion of 75 per cent of the dye in 2 hours. A bromsulfalein test of liver function showed no retention of the dye in the blood after 30 minutes. The blood bilirubin was normal, 0.3 milligram per 100 c.c. (monophasic). An alcohol test meal gave values for gastric acidity which if anything were somewhat above normal; the highest figure obtained for free hydrochloric acid was 98 points at 30 minutes after the alcohol had been given. No trace of gross blood was noted in the stools and although the benzidine test was reported as 1+, this lacks significance since the patient was not on a meat-free diet. A test of fragility of erythrocytes showed hemolysis to begin at a concentration of sodium chloride of 0.42 per cent and to be complete at one of 0.28 per cent. Biopsy of the skin was repeated and this again showed the presence of abnormal amounts of iron pigment, thus verifying the diagnosis of hemochromatosis.

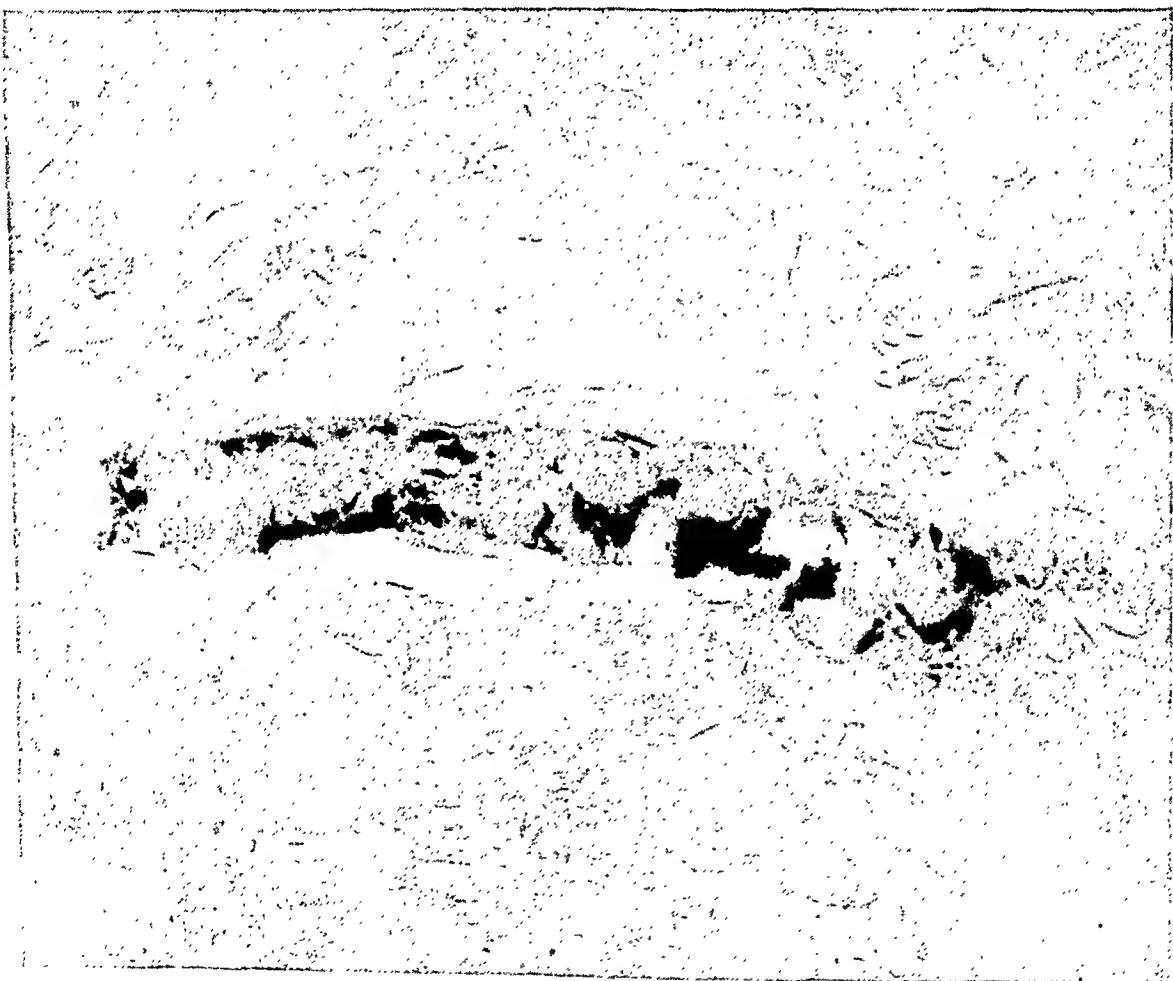


FIG. 2. High power view of sweat gland seen in lower mid-portion of section shown in figure 1. Note the marked accumulation of iron-containing pigment. (Potassium ferrocyanide, counterstain 0.5 per cent basic fuchsin;  $\times 300$ )

#### METHODS

The time of the experimental study was divided into nine periods of three days each (in the ninth period there were only two days). Preceding this, a five-day preliminary period on the diet outlined allowed time for adjustment to the diet and the ward routine. Balance studies were made on each three-day period and the iron con-

tent of the blood was determined at frequent intervals. During the month of study the patient was up and about and took daily walks but in general led a quiet life about the hospital.

*Food Intake.* The diet throughout the entire period of study was kept constant; not only was there no variation in the menu from day to day but as an added precaution the same preparations and brands—as of canned foods—were used from day to day. The dietary prescription was carbohydrate 230 grams, protein 73 grams, and fat 68 grams, furnishing 1824 calories per day.

The diet followed throughout the time of study is given in detail below:

	Grams		Grams
Asparagus	150	Bread	90
Peas	150	Unecda biscuits	2
Tomatoes, stewed	150	Beef cube for bouillon	1
Beans, string	150	Chicken, sliced white meat	45
Potato, baked	180	Steak, broiled tenderloin	45
Orange juice	300	Egg, scrambled	45
Banana	100	Butter	25
Applesauce	140	Cream, 20 per cent	60
Oatmeal (dry weight)	15	Milk	360

The food was cooked either in aluminum or earthenware utensils and often served in the same vessel in which it was cooked. Distilled water was used for drinking.

Aliquots of food for analysis were taken on one day of each three-day period. One-fifth by weight of each article was placed in a large evaporating dish and sent to the laboratory. Of the seven food aliquots thus analyzed the maximum variation of iron content between any two lots was 4.2 milligrams. The average figure obtained by our analyses was 50.7 milligrams per three-day period. From figures given by Sherman<sup>6</sup> the calculated iron intake for a three-day period was 53.3 milligrams, a difference of only 2.6 milligrams from the figure obtained by analysis.

*Collection and Preparation of Feces for Analysis.* The feces for each three-day period were marked off by the appearance of carmine which was given to the patient each third afternoon at 3 p.m. With the exception of the first two periods, the results of which were averaged because of an error in the administration of the carmine, there was no difficulty in observing the end of each period. The carmine taken at 3 p.m. was always evident in the evacuation of the following morning. The feces for each day were collected in a large new enamel pail and sent at once to the laboratory where they were transferred by means of distilled water to a large evaporating dish which was kept on the steam bath, the entire feces for one period being all transferred to one evaporating dish.

After complete drying, which usually required three to four days, the entire mass was ground to a fine powder with mortar and pestle. Weights taken before and after grinding showed almost invariably a loss of not more than 1 per cent. There was never any difficulty encountered either in getting the material completely dry or in powdering. Five-gram portions of the mixed powdered material were taken for iron analyses.

*Collection and Preparation of Urine for Analysis.* The urine was collected in 24-hour quantities and sent to the laboratory where it was accurately measured, preserved with a known quantity of toluol and transferred to a carboy containing the urine for that period. The entire quantity was acidified with a known volume of hydrochloric acid, thoroughly mixed and sufficient of the mixed lot saved for analyses.

*Reagents Used.* All reagents used were as nearly as possible free from iron. Special iron-free hydrochloric acid was used throughout the experiment. The nitric

acid used contained according to analysis no iron to the fourth decimal place. The best sodium thiocyanate we could obtain was Baker's C.P. analyzed which contained according to analysis 0.00015 per cent iron. Five c.c. of a 20 per cent solution (the quantity used in the determination) made from this salt would theoretically contain then only 0.001 milligram. By actual determination 5 c.c. of a 20 per cent solution showed the barest perceptible tinge of color. Since both standard and unknown would be similarly contaminated any error from this source was considered entirely negligible.

Blank determinations were made using the same quantities of reagents as used in each set of analyses and in no case was sufficient color obtained to be readable against the weak standard.

The distilled water used came from a copper-lined distilling apparatus and was conducted through copper pipes to a glass carboy. A determination made on both 500 c.c. and 1 liter portions evaporated to dryness gave essentially negative results.

During the course of the experiment the laboratory was freed completely from any possible source of contamination. All glassware used was washed in 10 per cent hydrochloric acid before using.

The evaporating dishes used for the drying and ashing processes were of "sillimanite." They were guaranteed to stand a temperature of 1400° C. with no deleterious effect. Only at the very end of our analyses did any of the dishes show signs of any erosion and even then no discrepancy in results could be noted between determinations carried out on these slightly eroded dishes and new ones.

*Chemical Methods.* The method employed for the determination of iron was the Elvehjem procedure as modified by Farrar.<sup>7</sup> Known aliquots of material were covered with iron-free calcium carbonate and ashed in an electric furnace at a temperature of 500° C.  $\pm$  25°. The ashed material was extracted with hydrochloric acid, hydrolyzed in a hydrochloric acid solution and just enough concentrated nitric acid added at the end of the period of hydrolysis to insure complete oxidation of all iron to the ferric condition. The final solution was transferred to a volumetric flask, made up to a definite volume and iron determined colorimetrically according to the method of Kennedy<sup>8</sup> on a suitable aliquot. Two standards were used, one containing 0.1 mg. iron per c.c. prepared from pure ferrous ammonium sulphate oxidized with potassium permanganate according to Elvehjem and Hart<sup>9</sup> and another containing 0.01 mg. iron per c.c. prepared from the strong standard by dilution. Analyses were carried out always in duplicate and frequently in triplicate.

*Analysis of Feces.* All analyses on feces were made as outlined above by ashing 5-gram portions of the powdered material. Usually it was found necessary to ash a second time in order to obtain a satisfactory residue. In such cases the acid filtrates from each ashing were combined before hydrolysis and oxidation took place. The final solution in each case was made to a volume of 100 c.c. and usually 5 c.c. used for the colorimetric determination.

*Analysis of Urine.* Urine analyses were made on 500 c.c. aliquots of the acidified three-day sample. The urine was evaporated to dryness on the steam bath and the dried residue ashed as outlined above. One ashing was always sufficient to yield a homogenous light gray ash. The final hydrochloric acid solution was made to a volume of 100 c.c. and 20 c.c. used for the colorimetric determination. This quantity contained sufficient iron to be easily comparable with the weak standard containing 0.01 mg. iron per c.c.

*Analysis of Food.* The aliquot representing one-fifth of a day's diet was dried on the steam bath until no appreciable moisture was apparent. Then 75 to 100 c.c. of concentrated nitric acid were added in *small portions* until a homogenous yellowish mixture was obtained. The yellowish mass was evaporated until the volume became sufficiently small to permit easy transfer to a smaller evaporating dish. The larger

dish was washed out several times with small quantities of distilled water to which a few cubic centimeters of concentrated hydrochloric acid had been added, all washings being added to the original contents. Evaporation was then continued until the mass became quite dry. It was then covered with 2 grams of iron-free calcium carbonate and ashed. Two and sometimes three ashings were required to obtain a satisfactory residue. The acid filtrates were combined and made up to a volume of 250 c.c. For hydrolysis, 25 c.c. portions were diluted to about 150 c.c. and boiled 30 to 40 minutes or until the volume was reduced to about 10 c.c. at which point oxidation was brought about by the addition to the hot solution of a few drops of concentrated nitric acid. The oxidized hydrolysate was made up to a volume of 50 c.c. and 20 c.c. used for the colorimetric determination. Evidence that hydrolysis and oxidation were complete under these conditions was afforded by obtaining essentially identical colorimetric determinations on different hydrolysates produced by variation of the time element, dilution and acidity.

*Blood Analysis.* One c.c. samples of oxalated blood (always obtained with the patient in the fasting state) were dried and ashed using 0.5 gm. of calcium carbonate. One ashing was usually sufficient. Hydrolysis, oxidation and colorimetry were carried out as previously described. The final volume in each case was 100 c.c., 20 c.c. of which were used for the analysis.

Other chemical methods employed were as follows: Titratable acidity of urine, Henderson and Palmer<sup>10</sup>; ammonia in urine, Folin permutit colorimetric procedure<sup>11a</sup>; total nitrogen in urine, Folin micro Kjeldahl colorimetric procedure<sup>11b</sup>; creatinine in urine, Folin.<sup>11c</sup>

## RESULTS

In table 1 are presented the results of the balance studies carried out in four three-day periods during which no medication was given except for the daily administration of insulin and two Squibb's halibut liver oil capsules (plain). (These capsules were found on analysis to contain no iron.) As stated before, due to an error in collection, Period I included the feces of four days whereas Period II included those of two days. Hence the results for the first two periods have been averaged.

It is evident that the patient was in slightly positive iron balance throughout the time of study, retaining from 2.2 to 7.7 mg. of iron per three-day period or from 0.7 to 2.6 mg. per day (average, 1.8 mg. per day).

Following these basic observations, during five subsequent periods a study of the effect of acidosis upon the iron balance was attempted. Our purpose was to discover any possible influence of such an acidosis upon the mobilization of iron in the body. Unfortunately the results secured were largely invalidated by two factors: (1) Not enough time was available for developing a significant acidosis (ammonium chloride was used in gradually increasing dosage) and (2) when the ammonium chloride tablets were analyzed at the conclusion of the study, it was found that the "enteric" coating was rich in iron so that each 0.5 gram tablet furnished 8.27 mg. of iron. However, the results are not without interest and so are presented in table 2.

It will be noted that despite the mild acidosis, relatively large amounts of iron were retained in the body. Whether the somewhat lower values obtained during Periods VII, VIII and IX as compared with those during

TABLE I  
Results of Studies of Iron Metabolism without Special Medication

Period	Dates (incl.) 1936	Blood Findings			Urinary Findings (other than iron)			Iron Metabolism (All values expressed per 3-day period)				
		Whole Blood Iron mg. per 100 c.c.	Hemo- globin per cent*	Erythro- cytes per cu. mm.	NH <sub>3</sub> Nitrogen gm. per 24 hrs.	Total Nitrogen gm. per 24 hrs.	Creat- inine gm. per 24 hrs.	Intake	Output			
I	Oct. 30					10.6	0.91	50.7	1.1	55.6	Average = 44.5	+ 6.2
	Oct. 31											
	Nov. 1											
II	Nov. 2					10.8	0.96	50.7	1.6	30.7	43.0	+ 7.7
	Nov. 3											
	Nov. 4		88	4.44								
III	Nov. 5					10.4	0.91	50.7	1.1	41.9	48.5	+ 2.2
	Nov. 6											
	Nov. 7											
IV	Nov. 8	44				10.8	0.95	50.7	1.2	47.3	45.3	+ 5.4
	Nov. 9											
	Nov. 10		85	4.38	0.27							
Averages: Per 3-day period								50.7	1.3	44.0	15.1	+ 1.8
Per day								16.9	0.4	14.7		

\* Newcomer glass standard; 100 per cent = 16.92 grams hemoglobin.



TABLE II  
Results of Studies of Iron Metabolism During Administration of Ammonium Chloride \*

Period	Date 1936	Blood Findings				24-hour Amount Urinary Findings (other than iron)				Iron Metabolism (All values expressed in mg. per 3-day period)				
		Iron whole blood mg. per 100 c.c.	Hemo-globin per cent	Erythro-cytes millions per cu. mm.	Plasma CO <sub>2</sub> vols. per cent	Titrat-able Acidity c.c. normal acid	Ammo-nia Nitro-gen gm.	Total Nitro-gen gm.	Creat-inine gm.	Intake		Output		Balance mg.
V	Nov. 11	44				35.0	0.26							
	" 12					34.1	0.57	12.1	1.02					
	" 13	45			51	31.5	0.57			198.5	249.2	1.2	145.0	+103.0
VI	" 14					33.8	0.57							
	" 15					34.6	0.70	12.1	1.02					
	" 16	43			53	32.6	0.76			264.6	315.3	1.3	199.0	+115.0
VII	" 17					30.6	0.73							
	" 18		82	4.14		43.9	1.05	12.6	0.99					
	" 19					37.8	1.11			297.7	348.4	1.3	274.5†	+ 72.6
VIII	" 20				45	34.2	1.34							
	" 21					32.9	1.27	13.4	1.03					
	" 22	46				40.7	1.38			297.7	348.4	1.5	299.0	+ 47.9
IX†	" 23				46	33.6	1.41							
	" 24	47	84	4.18		28.4	1.28	13.5	0.91					
	" 25				50					297.7	348.4	1.3	270.0	+ 77.1

\* The ammonium chloride was administered in 0.5 gram tablets, the enteric coating of which was later found to contain on the average 8.27 mg. of iron per tablet.

† The feces were lost for one day of this period. The value obtained for the remaining 2 days, 183.0 mg., was multiplied by 3/2 to obtain 274.5 mg.

‡ This was a 2-day period. The values for iron intake and output have been multiplied throughout by 3/2.

Periods V and VI are significant, is difficult to say. It is interesting that throughout the entire study (see tables 1 and 2) the amount of iron excreted in the urine was quite constant, varying only from 1.1 to 1.6 mg. per three-day period.

### DISCUSSION

The most significant findings in the present report concern the iron balance in the 12 days during which the patient was on an ordinary liberal diabetic diet (containing a normal amount of iron) without medication of any type likely to influence iron metabolism. Under such conditions, with an intake of 16.9 mg. of iron each day, an average of 1.8 mg. was retained. This figure does not differ materially from that reported by others for normal individuals<sup>12, 13, 14, 15</sup> or for patients with hemochromatosis.<sup>2, 3, 4, 5</sup>

The small amount of iron retained daily is in keeping with the theory supported by Sheldon<sup>16</sup> and Dry and Wilder<sup>17</sup> to the effect that hemochromatosis is an "inborn error of metabolism" characterized by the slow and gradual, yet abnormal, accumulation of iron in the tissues over a period of years, probably a lifetime. Such an assumption seems necessary in order to reconcile this slow rate of deposition with the fact that the tissues of individuals dying with hemochromatosis contain large stores of iron. Thus Sheldon states that the total iron content of the body of such cases ranges from 25 to 50 gm. as compared with the normal of about 3 gm.<sup>18</sup> Taking the figure obtained with our patient as an example, one finds on calculation that if 1.8 mg. of iron is retained daily during a lifetime of 50 years, a total of slightly less than 33 grams would accumulate.

One other possibility is suggested by the results of Fowler and Barer.<sup>5</sup> In one of their patients regarded as having hemochromatosis in an early stage, a greater amount of iron was retained per day, 5.42 mg., than in three other cases of hemochromatosis or in two cases of diabetes mellitus without hemochromatosis. The possibility is suggested that in the earlier stages of the disease iron is retained in excessive amounts not demonstrable later. As Fowler and Barer themselves point out, however, their results can be taken only as suggestive since the patient was studied for only one six-day period. The interpretation of this finding must await confirmatory evidence.

In the second part of our own study in which ammonium chloride was given, it is noteworthy that neither the mild acidosis nor the increased intake of iron (supplied by the enteric coating of the tablets of ammonium chloride) caused any change in the output of iron in the urine. This value remained remarkably constant throughout the entire study. Our patient responded to an increased iron intake with an increased retention as has been true with subjects studied by others.<sup>4, 5, 12, 13</sup> Worthy of note is the fact that during the last three periods, less iron was retained than during the first two, suggesting that the limit of the body for retention had been approached. In making any interpretation, however, one must keep in mind the mild acidosis which existed.

Some comment is needed regarding the values obtained for blood iron. They ranged from 43 to 47 mg. per 100 c.c. of whole blood and were thus well within the range found by Murphy, Lynch and Howard<sup>10</sup> in normal individuals. These workers found the average iron content of whole blood in normal young men to be 44.84 mg., in normal young women 42.48 mg., and in a group of 60 persons of both sexes and of varying age with an essentially normal blood (10 of the 60 had diabetes mellitus) 42.74 mg. per 100 c.c.

### SUMMARY

1. Studies are reported of the iron metabolism in a patient with hemochromatosis, a man aged 50.9 years with well-marked diabetes of 5.8 years' duration.

2. During four periods of three days each, it was found that with an average intake of 16.9 mg. of iron a day there was an average excretion of 0.4 mg. per day in the urine and 14.7 mg. per day in the feces, making a total output of 15.1 mg. per day and an average daily retention of 1.8 mg.

3. Studies designed to discover the effect of acidosis upon the mobilization of iron were inconclusive.

4. Values for the iron content of whole blood were within normal limits, ranging from 43 to 47 mg. per 100 c.c.

5. The findings are interpreted as supporting the theory that in hemochromatosis the abnormal retention of iron takes place slowly over many years of time, perhaps the lifetime of the individual. The possibility remains open, however, that in the earlier stages of the disease, retention of iron may take place at a more rapid rate than that evident in the patient studied.

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# THE NATURE OF ARTERIAL HYPERTENSION WITH SPECIAL REFERENCE TO THE RÔLE OF THE KIDNEY \*

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SINCE cardiac output,<sup>1</sup> blood volume,<sup>2</sup> and blood viscosity<sup>3</sup> are normal in patients with hypertension, the only remaining factor that might produce the elevated blood pressure is an increased peripheral resistance. This increased resistance is presumably generalized throughout the systemic circulation, and is the result of vascular hypertonus<sup>4</sup> confined to the arterioles although the small arteries may also be involved.<sup>5</sup>

The generalized arteriolar hypertonus responsible for hypertension could theoretically be produced by increased sympathetic vasomotor impulses or by circulating substances having a direct or indirect constrictor action on the arterioles.

Hypertension may be produced experimentally by means of renal ischemia,<sup>7</sup> ureteral obstruction,<sup>8</sup> removal of large amounts of kidney substance,<sup>9</sup> and by chemical,<sup>10</sup> serologic<sup>11</sup> and roentgenological<sup>12</sup> renal injuries. Complete unilateral or bilateral nephrectomy is not followed by hypertension.<sup>13</sup> It seems unlikely that a renal nervous mechanism is the cause since it has been found that denervation of the kidneys<sup>14</sup> or sympathectomy<sup>15</sup> does not prevent or relieve the hypertension induced by renal ischemia. Indeed, hypertension may be produced in dogs by ischemia of a kidney transplanted to the neck<sup>16</sup> or to the leg.<sup>17</sup> Goldblatt<sup>18</sup> has shown that clamping both renal arteries is followed by hypertension only if the renal veins are patent. This type of hypertension then is dependent upon a substance which is elaborated in the kidney and carried in the blood stream, and has a direct or indirect constrictor action on arterioles.

Since a pressor substance has been found to exist in normal kidneys<sup>19</sup> the theory that renal hypertension results from the humoral accumulation of this substance seems worthy of consideration. This view has been suggested in the past especially by Hartwich<sup>20b</sup> and Shaw<sup>20a</sup> but the evidence in favor of it has not been convincing.‡ It therefore seemed of interest to

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A preliminary report of this paper has appeared:

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† Work done during the tenure of Richard and Ella Hunt Sutro Fellowships.

From the Medical Service of Dr. B. S. Oppenheimer and the Laboratory Division of The Mount Sinai Hospital, New York City.

‡ Hartwich<sup>20b</sup> ligated the renal artery and vein of one dog. The pressed juice of the necrotic kidney gave pressor effects but he was unable to determine whether or not this pressor effect was greater than that of the normal kidney of this animal or that of other kidneys of normal dogs. Hartwich did not measure the blood pressure of this animal but it is now known that ligation of the renal artery and vein is not followed by hypertension.<sup>18</sup>

learn whether extracts of kidneys taken from normal and from hypertensive animals differed in their content of pressor material.

### PRESSOR EFFECTS OF EXTRACTS OF KIDNEYS FROM HYPERTENSIVE DOGS

Goldblatt and his co-workers<sup>7</sup> have shown that hypertension may be produced in dogs by constriction of one renal artery. A comparison, therefore, of the pressor effects of extracts made from the ischemic kidney with that of those prepared from the contralateral kidney from such an animal when hypertension has developed would appear to be of interest. Since the hypothetical agent would presumably be water soluble and since a water soluble renal pressor substance has been described, simple saline extracts seemed most suitable for the purpose.

Unilateral renal ischemia was produced in 30 dogs by means of the Goldblatt clamp. The blood pressure was measured by direct puncture of the femoral artery. A significant rise in blood pressure occurred in only 17, the average rise being 32 mm. mercury. The remaining animals were discarded. When the blood pressure, measured at frequent intervals after the operation, had risen significantly the animal was sacrificed by injecting chloroform intravenously. This generally took place in one to four days after constricting the renal artery. The operated and the unoperated kidneys were removed, weighed, and extracted separately.

The extracts were prepared in the following manner. All superfluous tissue was cut away and the capsule stripped off. The kidney was passed through a meat grinder, weighed and ground in a mortar for two minutes. One c.c. of physiological saline was added to each gram of tissue and the mixture ground for another two minutes and then placed in a mechanical shaker for a half hour. It was then centrifuged for 10 minutes and the supernatant fluid filtered.

The extracts of the ischemic and of the control kidney of the same animal were tested on cats and dogs anesthetized with nembutal and on unanesthetized dogs with van Leersum (carotid) loops. In the case of the anesthetized animals, 3 to 5 c.c. of the extracts to be tested were injected intravenously, and the effect upon carotid pressure noted. At least two animals were used for each set of comparisons.

In the case of the unanesthetized dogs, after a number of days of preliminary training, the animal was placed on its side for a 30 minute rest period. The systolic blood pressure was determined by palpation, two estimations being made every minute for a period of at least 15 minutes. The extract (5 to 7 c.c.) was then injected and further estimations of blood pressure made at similar intervals until the level, after rising, had begun to fall. The effect in millimeters of mercury was calculated as the difference between the mean of at least 30 readings before injection and the mean of an equal number obtained during a 15 minute period at the peak of the pressor response.

Injection of renal extracts into animals with or without anesthesia was usually followed by a transient fall and then a prolonged rise of blood pressure, returning gradually to the normal. Pressor effects were more constant, more pronounced and longer lasting in unanesthetized than in anesthetized animals, in some of the former being present for over two hours.

*Results.* In 16 out of 17 experiments the ischemic kidney had a greater pressor action than the control kidney of the same animal. In the remaining instance, no difference was noted. Depressor effects were produced by

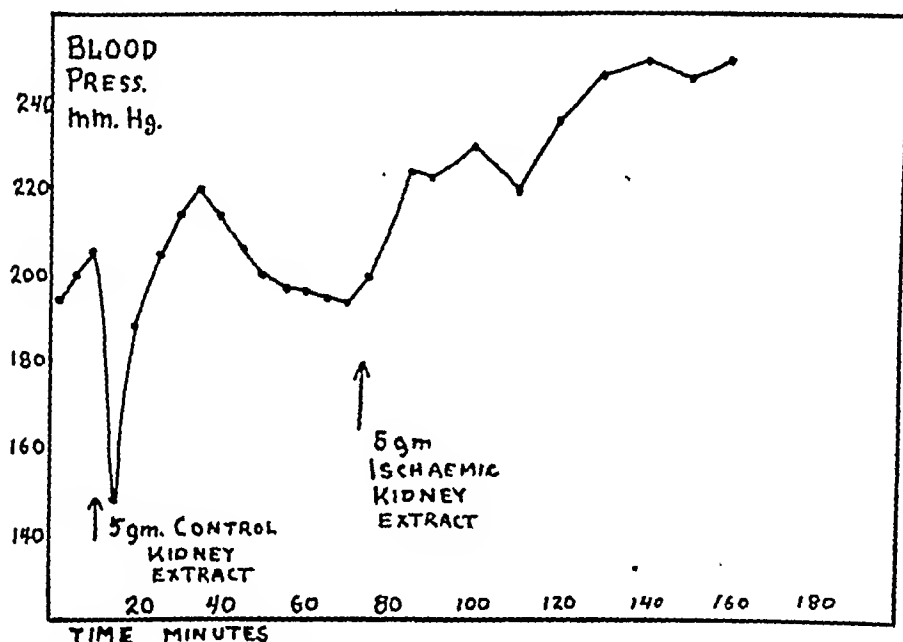


FIG. 1. Effect of intravenous injection of saline extracts of ischemic and unoperated kidney from dog with hypertension on blood pressure of unanesthetized dog with van Leersum loop.

11 of the control and only 2 of the ischemic kidney extracts. No rise in blood pressure occurred following the injection of 1 ischemic and 7 control kidney extracts (table 1, figure 1).

#### PRESSOR EFFECTS OF EXTRACTS OF ISCHEMIC SPLEEN AND MUSCLE

It is conceivable that the increased quantity of pressor substance found in ischemic kidneys might form in any tissue as a result of ischemia, and as such have no causal relation to hypertension. In order to test this possibility, similar observations were made on extracts of ischemic spleen and muscle. The splenic artery was constricted in four dogs and the femoral artery in two dogs by means of the Goldblatt clamp. After two to six days, saline extracts were made of the ischemic tissue and these were compared with extracts of normal spleen and muscle. In no instance did either the normal or ischemic spleen and muscle have a well defined pressor effect. Hypertension did not occur in any of the animals. This is in agreement with Goldblatt and his co-workers.<sup>7</sup>

TABLE I  
Pressor Effects of Extracts of Ischemic and Unoperated Kidneys from Dogs with Hypertension Produced by Unilateral Renal Ischemia

Dog	Days After Operation	Test Animal	Effect of Ischemic Kidney Extract			Effect of Normal Kidney Extract			Difference in Pressor Effect Between Ischemic and Unoperated Kidney mm. Hg
			Depressor Effect mm. Hg	Pressor Effect		Depressor Effect mm. Hg	Pressor Effect		
				mm. Hg	Duration min.		mm. Hg	Duration min.	
1		Anesthetized dog	0	40	15+	20	15	25	
2		Anesthetized dog	0	20	10	0	0	20	
3		Anesthetized cat	0	40	20	40	0	40	
57	4	Anesthetized cat	0	20	7	3	0	20	
54		Anesthetized dog	20	35	8	20	20	15	
78		Anesthetized cat	3	12	4	3	8	4	
89	13	Anesthetized hypertensive dog	0	15		15	15	10	
90	1	Anesthetized cat	0	0	0	0	0	0	
97	1	Unanesthetized dog	0	58	0	40	17	41	
107	3	Unanesthetized dog	0	25	120+	0	10	15	
93	2	Anesthetized cat	0	40	60	0	15	25	
111	2	Unanesthetized dog	0	27	50	0	21	6	
115	1	Anesthetized cat	0	30	42	18	0	30	
117	3	Anesthetized cat	0	36	90	0	25	3	
128	4	Anesthetized dog	0	20		10	0	11	
135		Anesthetized cat	0	20		35	0	20	
130		Anesthetized dog	0	16		40	12	4	



## DISCUSSION

These results demonstrate that saline extracts of ischemic kidneys from dogs, with experimental hypertension due to unilateral constriction of the renal artery, have greater pressor or lesser depressor effects than those of the opposite non-ischemic kidney. Since the hypertension in these animals must have a causal relationship to the ischemic and not the control kidney, it can then be concluded that the kidney which caused the hypertension possessed a greater quantity of pressor or lesser quantity of depressor substance. The greater pressor response elicited by the ischemic kidney extract was not due to a higher concentration of a normal amount of pressor material in a smaller mass since ischemic kidneys removed a short period after operation generally weighed more than the control specimens. Those removed at a later time often were smaller. Similar results have been independently obtained by Harrison, Blalock, and Mason<sup>21</sup> who produced hypertension in dogs by constricting the renal artery and by ureteral ligation.

In the present experiments the pressor substance from the ischemic kidneys was found to be more concentrated in the cortex than in the medulla, was destroyed by boiling for five minutes, and did not dialyze through a semipermeable membrane. Since similar properties have been attributed to extracts of normal kidneys,<sup>19</sup> the substance present in increased amounts in ischemic kidneys is probably similar to that first described by Tigerstedt and Bergman.<sup>19a</sup> The absence of increased pressor activity in ischemic spleen, renal medulla, and striated muscle suggests that this is not a non-specific property but is apparently peculiar to kidney cortex.

## PRESSOR EFFECTS OF EXTRACTS OF HUMAN KIDNEYS

In view of the findings in dogs, it seemed of importance to determine the pressor effects of extracts of kidneys from human beings with normal and elevated blood pressures. Kidneys were obtained after death from 21 subjects who had had hypertension of various types during life. Of these 12 were diagnosed as benign hypertension, five as malignant hypertension, two as chronic glomerulonephritis, and two showed pyelonephritic contracted kidneys with hypertension. The kidneys of 24 individuals of approximately the same age group, who had normal blood pressure during life and who had normal kidneys at autopsy, were extracted as controls. The organs were obtained at varying intervals after death. The extracts were prepared in the manner previously described. In these experiments it was necessary to test the pressor properties of extracts obtained over a period of several months under uniform circumstances on a test object which would remain as constant as possible over this period of time. Forty-one of the 45 extracts were tested in the manner described above on two trained unanesthetized dogs, with van Leersum (carotid) loops. Approximately the same number of extracts prepared from kidneys of normal and hypertensives were injected into each dog. The remaining four extracts,

of which two were from normal and two from hypertensive individuals, were tested on anesthetized animals. The equivalent of 7 grams of tissue was injected into the unanesthetized and 3 to 5 grams into the anesthetized animals.

*Results.* The average pressor effect of the 21 extracts from the kidneys of hypertensive patients was 26 mm. mercury (standard deviation of the mean—3.4 mm. mercury), with a range between 9 and 60 mm. mercury. The mean pressor effect of the 24 extracts in the non-hypertensive group was 14 mm. mercury (standard deviation of the mean 2.7 mm. mercury), the range being from 0 to 48 mm. mercury. No significant difference was noted in the depressor effects of the two groups (tables 2 and 3, figure 2).

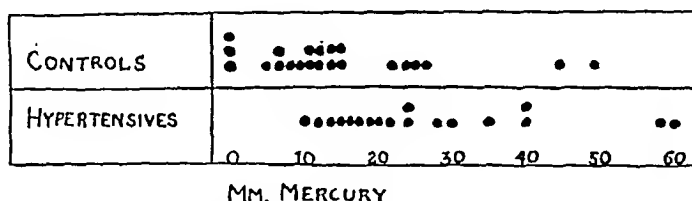


FIG. 2. Pressor effect in millimeters of mercury of saline extracts of kidneys from human beings.

The mean pressor effect of the 17 extracts from kidneys of patients with so-called essential hypertension (benign and malignant) was 23.8 mm. mercury (the standard deviation being 3.4 mm. mercury).

## DISCUSSION

It may be seen that considerable variation exists in both series, the extracts of some kidneys from patients who had marked hypertension during life producing only slight pressor actions, whereas others in the control group had marked effects.

It is possible that the variations observed may be in part at least due to complicating factors such as postmortem changes and manner of death. It was frequently impossible to obtain accurate weights of the kidneys and the patients. It is probable that in relation to body weight, the weights of the hypertensive kidneys were smaller than the control kidneys; and since the same amount of renal tissue was used in the case of both extracts, it is likely that in some instances the pressor material might have been present in normal amount but at the same time in greater concentration in the smaller hypertensive kidneys. The exclusion of the four severely contracted kidneys which were the only instances of so-called renal hypertension did not significantly alter the results. More work with purer, fresher extracts from kidneys of known weights must be done before final conclusions can be drawn.

It is not known whether the pathogenesis of human hypertension is the same as in experimental hypertension due to renal ischemia. The high

TABLE II  
Vasomotor Effects of Kidney Extracts from Human Beings with Hypertension

Case	Age	Sex	Blood Pressure	Diagnosis	Cause of Death	Kidney Function	Condition of Kidneys	Time Tested After Death*	How Tested	Result mm. Mercury		Duration of Pressor Effect in Minutes
										De-pressor Effect	Pressor Effect	
1	58	F	190/100	Benign hypertension	Heart failure	Normal	Congested. Benign nephrosclerosis	24 hrs.	Anesthetized dog	25	15	15
2	30	M	190/100	Benign hypertension	Bronchopneumonia	Normal	Benign nephrosclerosis	24 hrs.	Anesthetized cat	10	16	45
3	45	F	280/160	Malignant hypertension	Bronchopneumonia	Moderately impaired	Malignant nephrosclerosis	24 hrs.	Anesthetized dog	0	10	10
									Anesthetized cat	0	9	
									Unanesthetized dog	50	40	Over 160
4	39	M	160/100	Chronic glomerulonephritis	Uremia	Severely impaired	Chronic glomerulonephritis. Pyelitis	48 hrs.	Unanesthetized dog with van Leersum loop	100	28	80
5	52	M	190/110	Benign hypertension	Bronchopneumonia	Normal	Benign nephrosclerosis	48 hrs.	Unanesthetized dog with van Leersum loop	80	40	Over 160
6	?	F	210/110	Pyelonephritis	Heart failure	Moderately impaired	Pyelonephritic contracted kidneys	24 hrs.	Unanesthetized dog with van Leersum loop	50	35	170
7	67	F	260/110	Benign hypertension	Cerebrovascular accident	Moderately impaired	Benign nephrosclerosis. Congestion	48 hrs.	Unanesthetized dog with van Leersum loop	60	58	Over 90
8	65	F	190/100	Benign hypertension	Heart failure	Normal	Benign nephrosclerosis. Congestion	48 hrs.	Unanesthetized dog with van Leersum loop	5	24	Over 60
9	63	F	190/100	Benign hypertension	Carcinoma of stomach	Normal	Congestion Benign nephrosclerosis	12 hrs.	Unanesthetized dog with van Leersum loop	0	19	80
10	64	M	210/110	Benign hypertension	Carcinoma of pancreas	Normal	Benign nephrosclerosis. Bile-stained	52 hrs.	Unanesthetized dog with van Leersum loop	55	22	100

\* These figures are accurate within 12 hours.

TABLE II—Continued

Case	Age	Sex	Blood Pressure	Diagnosis	Cause of Death	Kidney Function	Condition of Kidneys	Time Tested After Death*	How Tested	Result mm. Mercury		Duration of Pressor Effect in Minutes
										De-pressor Effect	Pressor Effect	
11	28	F	190/110	Chronic glomerulonephritis	Uremia	Severely impaired	Chronic glomerulonephritis	48 hrs.	Unanesthetized dog with van Leersum loop	40	24	60
12	30	M	250/152	Malignant hypertension	Uremia	Severely impaired	Malignant nephrosclerosis	50 hrs.	Unanesthetized dog with van Leersum loop	50	17	Over 90
13	69	F	240/150	Benign hypertension	Cerebral thrombosis	Normal	Benign nephrosclerosis	48 hrs.	Unanesthetized dog with van Leersum loop	60	12	Over 60
14	67	M	240/132	Benign hypertension	Cerebral hemorrhage		Benign nephrosclerosis	24 hrs.	Unanesthetized dog with van Leersum loop	25	13	Over 80
15	43	F	240/150	Pyelonephritis hypertension	Uremia. Congestive failure	Severely impaired	Pyelonephritic contracted kidneys	4 hrs.	Unanesthetized dog with van Leersum loop	0	60	Over 170
16	44	F	280/190	Malignant hypertension	Uremia	Moderately impaired	Malignant nephrosclerosis	90 hrs.	Unanesthetized dog with van Leersum loop	30	16	20
17	52	M	260/160	Malignant hypertension	Uremia	Severely impaired	Malignant nephrosclerosis		Unanesthetized dog with van Leersum loop	0	20	50
18	51	F	180/95	Benign hypertension	Coronary thrombosis	Normal	Benign nephrosclerosis		Unanesthetized dog with van Leersum loop	70	30	Over 65
19	23	F	150/120	Libman-Sachs disease	Uremia	Impaired	Intraepillary glomerulonephritis	8 hrs.	Unanesthetized dog with van Leersum loop	0	13	40
20	52	M	160/90	Benign hypertension	Cerebral hemorrhage	Normal	Benign nephrosclerosis	24 hrs.	Unanesthetized dog with van Leersum loop	20	14	30
21	45	F	240/130	Benign hypertension	Uremia. Thrombosis of splenic artery	Impaired	Benign nephrosclerosis	24 hrs.	Unanesthetized dog with van Leersum loop	0	38	Over 50

\* These figures are accurate within 12 hours.

TABLE III  
Vasomotor Effects of Kidney Extracts from Human Beings with Normal Blood Pressure

Case	Age	Sex	Blood Pressure	Cause of Death	Condition of Kidneys	Time Tested After Death*	How Tested	Results mm. Mercury		Duration of Pressor Effect
								De-pressor Effect	Pressor Effect	
1	47	M	110/72	Coronary occlusion	Normal	24 hrs.	Anesthetized dog	60	0	
2	30?	M		Bullet wound	Normal	12 hrs.	Anesthetized cat	25	0	5 minutes
3	50?	M	120/70	Pulmonary embolism	Normal	48 hrs.	Anesthetized cat	40	10	
4	28	F		Subdural hematoma (traumatic)	Normal	48 hrs.	Unanesthetized dog van Leersum loop	35	0	50 minutes
5	36	M	120/80	Pulmonary embolism	Normal	24 hrs.	Unanesthetized dog van Leersum loop	80	26	40 minutes
6	66	M	120/70	Cirrhosis of liver. Mesenteric thrombosis	Normal	48 hrs.	Unanesthetized dog van Leersum loop	30	12	90 minutes
7	65	M	90/60	Peritonitis. Bronchopneumonia	Congested	12 hrs.	Unanesthetized dog van Leersum loop	20	11	Over 120 minutes
8	65	M	90/60	Shock. Luetic aortitis	Slight pyelitis	24 hrs.	Unanesthetized dog van Leersum loop	0	48	
9	62	M	90/60	Pneumonia	Normal	24 hrs.	Unanesthetized dog van Leersum loop	5	0	Over 60 minutes
10	54	M	120/70	Hemorrhage into peritoneal cavity. Cirrhosis of liver	Normal	48 hrs.	Unanesthetized dog van Leersum loop	50	8	Over 60 minutes
11	51	F	120/60	Mesenteric thrombosis	Normal	12 hrs.	Unanesthetized dog van Leersum loop	70	15	40 minutes
12	13	F	100/60	Peritonitis	Normal	12 hrs.	Unanesthetized dog van Leersum loop	0	12	Over 65 minutes
								0	25	Over 70 minutes
								40	7	40 minutes

\* These figures are accurate within 12 hours.

TABLE III—Continued

Case	Age	Sex	Blood Pressure	Cause of Death	Condition of Kidneys	Time Tested After Death*	How Tested	Results mm. Mercury		Duration of Pressor Effect
								De-pressor Effect	Pressor Effect	
13	62	M		Lobar pneumonia	Parenchymatous degeneration	12 hrs.	Unanesthetized dog van Leersum loop	0	10	Over 80 minutes
14	48	F		Pericarditis	Normal	12 hrs.	Unanesthetized dog van Leersum loop	15	12	60 minutes
15	9	F	80/60	Bronchopneumonia	Normal	12 hrs.	Unanesthetized dog van Leersum loop	25	0	60 minutes
16	38	F	80/60	Carcinoma of ovary	Normal	12 hrs.	Unanesthetized dog van Leersum loop	0	11	60 minutes
17	52	M	120/80	Carcinoma of pancreas	Normal	24 hrs.	Unanesthetized dog van Leersum loop	25	15	Over 60 minutes
18	26	M	96/68	Thrombophlebitis with abscesses	Normal	24 hrs.	Unanesthetized dog van Leersum loop	0	22	Over 60 minutes
19	42	F	130/80	Carcinoma of pancreas	Normal	10 hrs.	Unanesthetized dog van Leersum loop	25	0	
20	55	M	120/70	Pneumonia, Otitis media	Normal	24 hrs.	Unanesthetized dog van Leersum loop	0	44	60 minutes
21	14	M	120/80	Septicemia	Normal	18 hrs.	Unanesthetized dog van Leersum loop	15	24	Over 45 minutes
22	38	F	140/86	Asthma	Normal	24 hrs.	Unanesthetized dog van Leersum loop	20	7	20 minutes
23	42	M	120/60	Peritonitis, <i>B. welchii</i> infection	Normal	15 hrs.	Unanesthetized dog van Leersum loop	0	14	
24	68	M	126/80	Carcinoma of esophagus with metastases	Normal	8 hrs.	Unanesthetized dog van Leersum loop	25	0	

\* These figures are accurate within 12 hours.

incidence of arteriolar lesions in the kidney,<sup>22</sup> the persistence of vascular hypertonus following removal of vasoconstrictor tone,<sup>23</sup> and the occasional cure of hypertension following removal of a pathological kidney<sup>24</sup> suggest that hypertension in human beings results from a similar mechanism.

The demonstration of an increased amount of pressor substance in kidneys of hypertensives does not necessarily prove that this substance is the cause of the elevation in blood pressure. However, it is compatible with the hypothesis that hypertension is the result of an increased humoral accumulation of a pressor substance normally elaborated by the kidneys. The failure of hypertension to develop following renal ischemia in adrenalectomized animals and the protective effect of non-ischemic renal tissue indicate that other factors are concerned. Final proof would seem to reside in the finding of an increased quantity of this substance in the blood of hypertensive subjects.

### CONCLUSIONS

1. Hypertension was produced in 17 dogs by means of unilateral renal ischemia.

2. Saline extracts of the ischemic kidney produced greater pressor effects than extracts of the contralateral control kidney in 16 of the 17 experiments. Saline extracts of ischemic kidney also produced lesser depressor effects than extracts of the control kidneys.

3. Saline extracts of ischemic spleen and muscle did not have any pressor actions.

4. The mean pressor effect of saline extracts of kidneys from 21 patients who had hypertension of various types during life was greater than that of renal extracts from 24 subjects who had had normal blood pressures.

5. These observations are compatible with but do not prove the hypothesis that hypertension in man (both "essential" and "renal") and in animals is due to an increased humoral accumulation of a pressor substance normally elaborated by the kidney.

The authors want to thank Drs. B. S. Oppenheimer and Harry Goldblatt for aid and advice.

Since the completion of this work Pickering and one of the authors of this paper (M. P.) have determined the quantity of renin in hypertensive rabbits. Employing the method of assay and extraction recently described (PICKERING, G. W., and PRINZMETAL, M.: Some observations on renin, a pressor substance contained in normal kidney together with a method for its biological assay, *Clin. Sci.*, 1938, iii, 211), no significant increase in the amount of renin was found in kidneys of hypertensive rabbits.

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# VASOMOTOR EFFECTS OF BLOOD IN PATIENTS WITH HYPERTENSION AND ANIMALS WITH EXPERIMENTAL HYPERTENSION \*

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RECENT investigations have suggested that the abnormal vasoconstriction in animals and patients with persistent hypertension is due to a non-nervous and presumably chemical mechanism.<sup>1, 2, 3, 4, 5</sup> Increased amounts of a pressor substance have been demonstrated in saline extracts made from kidneys of dogs with renal hypertension and from kidneys of patients suffering from hypertensive disease.<sup>6, 7</sup> These observations are compatible with the hypothesis that such forms of hypertension are due to the humoral accumulation of a pressor substance of renal origin. This hypothesis would be verified by the demonstration of increased amounts of the substance in the blood stream in patients or animals with hypertension. Many workers have sought such circulating pressor materials. The literature has been adequately reviewed in several recent reports.<sup>8, 9, 10</sup> In general the results have been conflicting even when identical methods were employed. In view of these considerations it seemed important to look anew in the circulating blood stream.

The following experiments were carried out:

1. Cross transfusion between patients with hypertension and subjects with normal cardiovascular systems.
2. Comparison of the vasomotor effects of the plasma from patients with elevated and those with normal blood pressures by perfusion of the rabbit's ear preparation.
3. Comparison of vasoactive properties of blood taken from normal and hypertensive dogs by perfusion through tissues of dogs with experimental hypertension.
4. Study of the vasomotor activity of renal vein blood obtained from animals rendered hypertensive by means of renal ischemia.

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Preliminary reports of this paper have appeared:

FRIEDMAN, B., and PRINZMETAL, M.: Vasomotor effects of blood in hypertension, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxiv, 543.

PRINZMETAL, M., FRIEDMAN, B., and ROSENTHAL, N.: Nature of peripheral resistance in arterial hypertension, *Ibid.*, 1936, xxxiv, 546.

† Work done during the tenure of Richard and Ella Hunt Sutro Fellowships.

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CROSS TRANSFUSION OF BLOOD BETWEEN SUBJECTS WITH HYPERTENSION  
AND PATIENTS WITH NORMAL BLOOD PRESSURE

Høst<sup>11</sup> and Pickering<sup>12</sup> observed no elevation in blood pressure in the recipient following transfusion of as much as 700 c.c. of blood from donors with hypertension. Collins and Hoffbauer<sup>13</sup> likewise observed no pressor effect in normal dogs receiving large quantities of blood from dogs with experimental renal hypertension. In the following observation an interchange of large amounts of whole blood between patients with malignant hypertension and subjects with normal cardiovascular systems was effected by the method of cross transfusion. This experiment was done not only because of its theoretical implications but also because of its possible therapeutic value. If hypertension is due to the increased concentration of a pressor substance in the blood stream one would expect the hypertensive patient to have a fall in blood pressure consequent on dilution by the normal blood. Likewise, the individual with normal blood pressure should have an elevation of blood pressure because of the increased concentration of pressor material in the transfused blood of the hypertensive donor.\*

The subjects, of the same blood group, were kept in bed and the blood pressure determined daily for a period of one week. They were then placed head to head with the arms extended. Two Unger transfusion sets were used, both operated at the same speed so that a gradual mixture of the blood of the two patients was brought about without a change in blood volume in either one. This technic does not require anti-coagulants and lasts about 30 minutes. During the transfusions repeated auscultatory blood pressure determinations were made at the popliteal arteries of both subjects. Four such procedures were carried out, the amounts of blood exchanged being 500, 650, 1460, and 2000 c.c. In these experiments a certain amount of blood was necessarily transferred back to the original subject, especially during the later stage of the procedure. In order to find the ratio of transfused blood to the computed total circulating blood volume, Congo red was injected intravenously into the individual with normal blood pressure immediately before the transfusion of 2000 c.c. of blood. At the end of the transfusion 42 per cent of the total circulating dye of both subjects was found in the hypertensive individual. With this information and knowing the total blood volume of each subject, the ratio of transfused blood to total circulating blood volume was computed for each person.

In no instance was there a significant change in blood pressure in either the hypertensive or normal subject during or for a period of one week following the transfusion. (Figures 1A and 1B:)

It is possible that the failure to demonstrate a pressor substance in the blood of patients with malignant hypertension is due to its dilution by the tissue fluids of the recipient. It is also possible that malignant hypertension is not renal in origin and that an increased concentration of pressor substance occurs only in "renal" hypertension. Evidence has been obtained,

\*The subjects with normal cardiovascular systems had inoperable carcinomata.

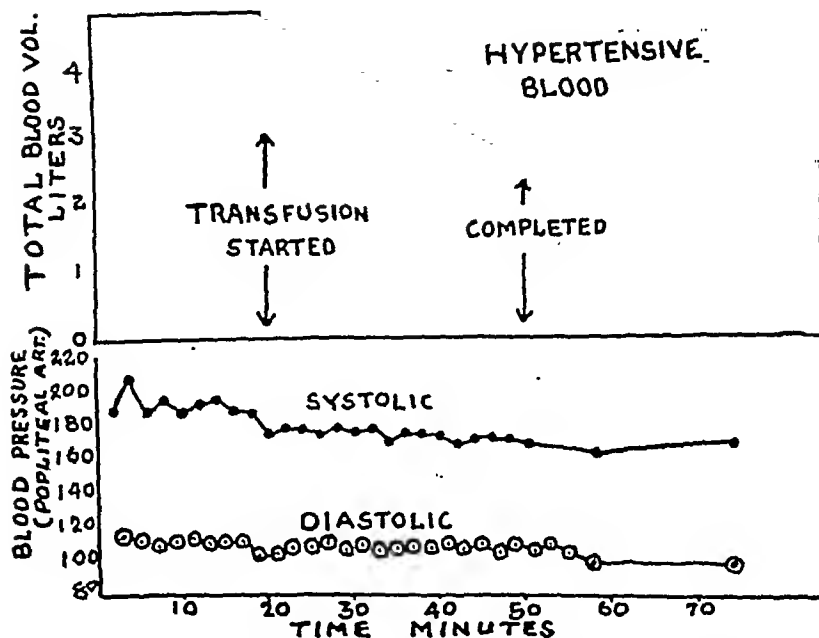


FIG. 1 A. Popliteal blood pressure of patient with carcinoma of the larynx and normal cardiovascular system receiving 2000 c.c. of blood from donor with malignant hypertension during cross-transfusion.

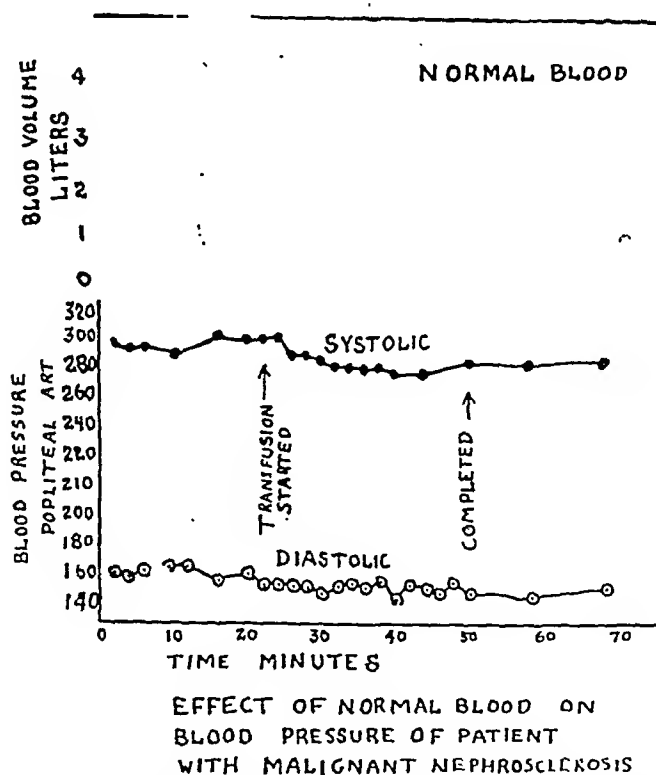


FIG. 1 B. Popliteal blood pressure of patient with malignant hypertension receiving 2000 c.c. of blood from donor with normal blood pressure during cross-transfusion.

however, that increased amounts of pressor substance may be present in the kidneys of subjects who had had "essential" hypertension (benign and malignant) during life.<sup>14</sup> Other methods were used which might overcome these difficulties.\*

#### DETERMINATION OF VASOMOTOR EFFECTS OF BLOOD OF PATIENTS WITH HYPERTENSION BY PERFUSION OF THE RABBIT'S EAR

The rabbit's ear preparation is very sensitive to known vasoactive substances and has been used as a test object by several workers, all of whom obtained pressor effects with blood from subjects with various types of hypertension. Kahlson and von Werz<sup>16</sup> found pressor substances in the blood of old patients with hypertension and also in patients suffering from febrile diseases. Kuri, Nakaya, Murakami and Okinaka,<sup>17</sup> using arterial blood with precautions to prevent oxidation, observed increased vasoconstrictor activity in patients with hypertension. They believed the vasoactive material to be epinephrine. Brand and Katz<sup>18</sup> detected pressor substances in patients with paroxysmal hypertension during the crises. The vasoconstrictor effect, like that of epinephrine, was prevented by ergotoxine. Volhard<sup>19</sup> reports the observations of Bohn who noted pressor properties in extracts prepared from the blood of patients with renal (pale) hypertension but not in those with "red" hypertension. Hantschman<sup>20</sup> on the other hand reported vasoconstrictor activity in all types of hypertension as well as in the blood of animals with experimental renal injuries.

To detect the presence of a hypothetical pressor substance it would seem most desirable to use blood with minimum of change and a test object with maximum sensitivity to known pressor substances. Concentration or extraction of the material although desirable cannot logically be performed until the chemical properties of the substance are known. For this reason whole undiluted blood plasma was used and perfused through the isolated rabbit's ear.

The method first described by Krakow and Pissemiski<sup>21</sup> consists of perfusion through the central artery of the amputated rabbit's ear attached to a long vertical glass tube which acts as a pressure gauge. Fluid is allowed to drip in at the top of the tube at a constant rate and forms a level in the tube. A change in the resistance of the vascular bed will be reflected by a change in the level of the fluid in the tube if the inflow remains constant. A Mariotte bottle did not give uniform inflow. For this purpose a constant volume pump<sup>22</sup> was found to be satisfactory.

Blood was collected from the antecubital veins of subjects with normal and elevated blood pressures, centrifuged, filtered, and used immediately. Heparin or citrate served as an anticoagulant. We have found that by this method one may detect

\* It was suggested that the failure of the blood pressure to rise in the normal subject might be due to the increased renal excretion of the hypothetical pressor substance by the normal kidney. For this reason, in one experiment, the urine of the individual with normal blood pressure was collected for 24 hours before and immediately following transfusion. Extracts were prepared and vasomotor effects compared according to the method of Capps and his co-workers.<sup>15</sup> No difference was noted between the extracts made from the urine excreted before and that immediately following the transfusion.

epinephrine in concentration of 1 to 100,000,000 and pituitrin in 1 to 150,000. The surface tension and viscosity of the plasma were measured since it is well known that these properties may affect the rate of flow. The ear was perfused first with Tyrode's solution until the tonus of the vessels became constant (50 to 60 minutes). Plasma was then introduced, alternating back and forth between that taken from the hypertensive and control patient. A few drops of Congo red added to one of the samples facilitated its detection as it entered the ear. Before terminating the experiment varying concentrations of pitressin, ephedrine, epinephrine, or guanidine were added to the plasma to test the reactivity of the preparation.

The vasomotor effect of the blood from 20 patients with various types of hypertension was compared with that of 20 patients with normal blood pressure. The former group consisted of eight subjects with benign hypertension, two with malignant hypertension, seven in various stages of glomerulonephritis, one with polycystic kidney disease, and two with hypertension associated with Cushing's syndrome. The plasma of three patients with acute glomerulonephritis was tested during the active phase of the disease when hypertension was present and following recovery when the blood pressure declined to the normal level, each case thus serving as its own control.

TABLE I

Vasomotor Effects of Blood from Patients with Hypertension as Compared with That of Subjects with Normal Blood Pressure Tested by Means of Perfusion of Rabbit's Ear

Type of Hypertension	Response with Respect to Normal			
	Pressor	Unchanged	Depressor	Total
Benign.....	1	4	3	8
Malignant.....	0	0	2	2
Glomerulonephritis				
Acute.....	1	0	3	4
Subacute or chronic.....	0	1	2	3
Polycystic kidney disease.....	0	0	1	1
Cushing's syndrome.....	0	0	2	2
	2	5	13	20

*Results* (Table 1). In 13 instances the plasma of the hypertensive subjects was depressor, in 2 cases pressor, and in 5 instances no differences were observed as compared with the plasma of normal individuals. In all three subjects with acute glomerulonephritis, the blood was depressor during the hypertensive phase of the disease. Following recovery, the depressor effect persisted in one instance, while in the other two the plasma became pressor with respect to that of control subjects. Figures 2*A* and *B* illustrate the findings in one experiment.

The changes could not be attributed to variations in viscosity or surface tension since these properties varied only slightly and in no consistent direction. Following the addition of minute amounts of known pressor sub-

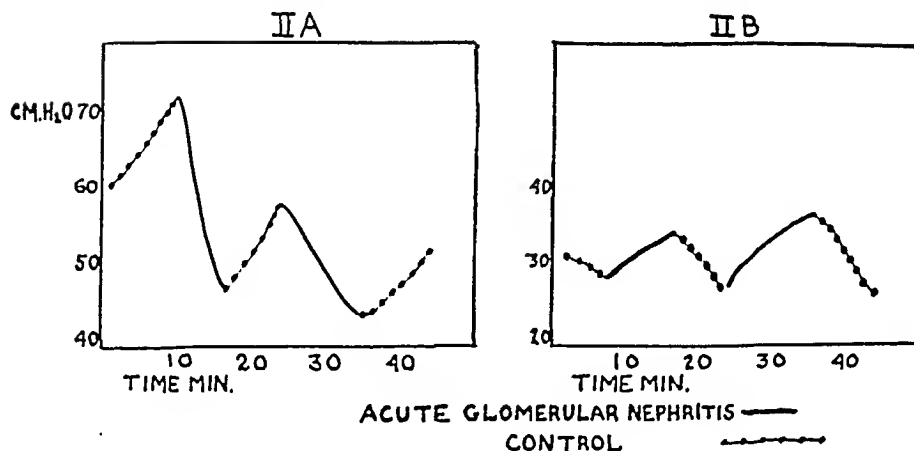


FIG. 2 *A* and *B*. Vasoconstrictor effect on the rabbit's ear of plasma of patient with acute glomerulonephritis compared with that of a normal subject.

*A*. April 13, 1936. Depressor effect during hypertensive phase. Blood pressure 160/110.

*B*. April 23, 1936. Pressor effect in recovery phase. Blood pressure 130/80.

stances (epinephrine 1 to 100,000,000) the plasma from both hypertensive and control patients invariably developed vasoconstrictor properties.

#### VASOMOTOR EFFECTS OF PLASMA FROM A SUBJECT WITH HYPERTENSION DUE TO ADRENAL PHEOCHROMOCYTOMA

It is well known that certain tumors of the adrenal medulla are associated with hypertension of a paroxysmal nature. Since epinephrine has been found in the tumors,<sup>23</sup> it has been assumed that the hypertension in patients with pheochromocytomata is due to hyperepinephremia. This type of hypertension would seem to be physiologically similar to that induced by the administration of epinephrine. A study of the vasomotor properties of the blood of such patients using the perfusion method previously described is of theoretical and some practical interest, since with this method no pressor substance has been detected in the blood of subjects with the ordinary types of hypertension. We have had the opportunity to study such a patient.\*

A 26-year-old woman for a period of 7 years had had recurrent attacks characterized by hypertension (300 plus systolic, 160 to 200 diastolic); tachycardia; throbbing headache; palpitation; choking sensations; numbness and blanching of the fingers, toes, and tip of the nose; profuse perspiration and tenseness. The attacks could be precipitated by exertion and lasted from 5 to 15 minutes. Between attacks the blood pressure level was slightly elevated (160/120). At operation a large adrenal tumor was found and removed. The tumor showed the typical histological appearance of a pheochromocytoma, and epinephrine-like substances were extracted and demonstrated by chemical and physiologic tests. Following operation the attacks disappeared and the blood pressure fell gradually over a period of several days to a

\* This case has been reported in full elsewhere:

BEER, E., KING, F. H., and PRINZMETAL, M: Pheochromocytoma with demonstration of pressor (adrenalin) substance in the blood preoperatively during hypertensive crisis, *Ann. Surg.*, 1937, *cvi*, 85.

level of 130/90 where it has remained. The patient has been symptom-free for a period of 12 months. (October 1937.)

The vasomotor effect of plasma collected during an attack of hypertension (blood pressure 300 plus systolic, 200 diastolic mm. mercury) was tested. Following operation when the blood pressure had fallen to 130/90 the plasma was again tested. During the attack of hypertension, the plasma had a very marked pressor effect compared with that of a control subject.

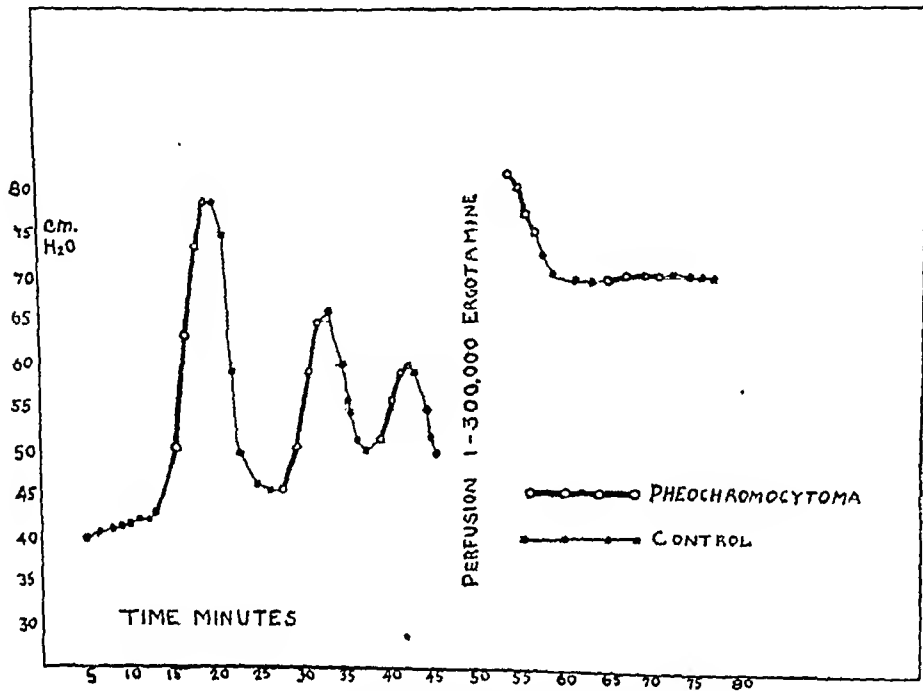
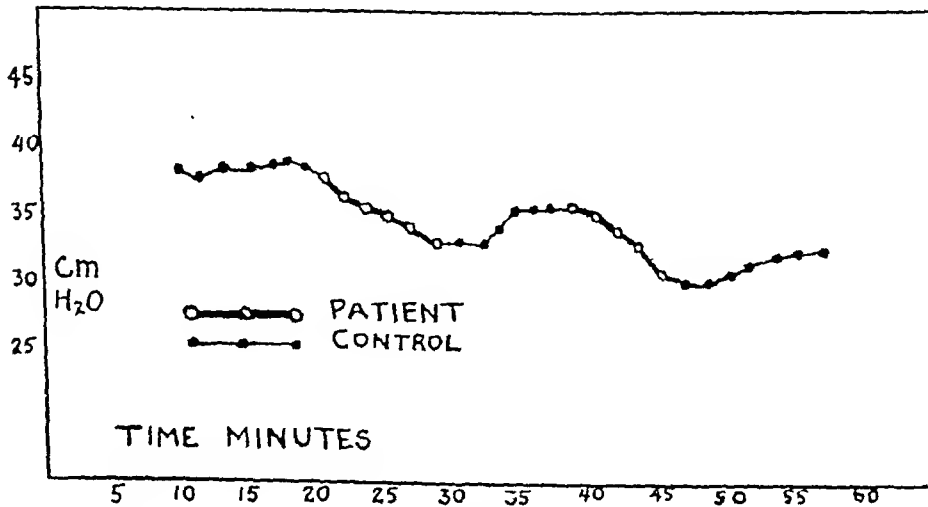


FIG. 3 A and B. Vasomotor effect on the rabbit's ear of plasma of patient with hypertension due to pheochromocytoma as compared with that of a control subject.

A. During a paroxysm of hypertension (blood pressure 300 plus/200) before operation showing pressor effect abolished by ergotamine.



B. After operation blood pressure 130/90 showing relative depressor effect.



This pressor effect was prevented when the rabbit's ear had been previously perfused with ergotamine tartrate (1:400,000). Following operation, when the blood pressure was normal, the pressor effect of the blood had entirely disappeared (figure 3).

*Discussion.* The results demonstrate that the method is capable of detecting the presence of circulating epinephrine in concentrations sufficient to cause hypertension. It further serves to differentiate this rare type of hypertension from the ordinary types previously described.

The failure to detect such substances in the blood of patients with ordinary types of hypertension is evidence against the hypothesis that an increased concentration of circulating epinephrine-like substances is responsible for the elevation in blood pressure in these cases.

#### THE PERFUSION OF TISSUES OF HYPERTENSIVE DOGS WITH BLOOD FROM NORMAL AND HYPERTENSIVE DOGS

The methods previously employed in testing for a pressor substance involved the use of tissues of normal animals as test objects. It seemed possible that such a substance might act only on vessels of animals with hypertension. For this reason other experiments were performed in which the tissues of hypertensive dogs were used as test objects. Furthermore, in these experiments the blood and test object were taken from animals of the same species.

*The Perfusion of Hypertensive Dogs' Tails.* Hypertension was produced in dogs by constricting both renal arteries.<sup>24</sup> After the blood pressure had risen, the animals were heparinized, bled from the carotid artery and their tails amputated. The central artery of the tail was then cannulated and perfused by means of a constant volume pump with whole heparinized blood heated to body temperature. The pressure required to force a given volume of blood through the tail was recorded. The initial level of perfusing pressure was adjusted to approximate the level of the mean blood pressure of the dog prior to bleeding. The vasomotor effects of the animal's own (hypertensive) blood were compared with those taken from normal dogs. If hypertension were due to an increased concentration of a pressor substance, normal blood should result in dilatation of the hypertonic vessels.

The experiment was performed five times. In three instances the blood taken from the hypertensive dog was depressor, in one case pressor as compared with normal blood, and in the remaining instance no difference was observed. The addition of minute amounts of epinephrine to the hypertensive animals' blood in four experiments caused it to become pressor when it was not originally so.

*Perfusion of Hypertensive Dogs' Legs.* These experiments were carried out by the technic of retrograde perfusion described by Cattell<sup>25</sup> and modified by Harrison and Burch.<sup>26</sup> The method permits perfusion of tis-

sues at any desired pressure at the same time insuring an adequate blood supply between periods of perfusion.

A cannula with opening directed centrally was placed in the femoral artery distal to the branching of the profunda femoris. The cannula was connected to a heating coil warmed to body temperature and to a graduated burette in which the pressure was regulated by a pressure bottle. During periods of perfusion a clamp was placed on the femoral artery proximal to the profunda branch, the blood flowing from the burette through the heating coil and cannula up the femoral artery and into the profunda and other branches of the femoral artery between the clamp and cannula. Between periods of perfusion the clamp was applied to the femoral artery just central to the cannula, thus reestablishing the normal circulation to the tissues under observation.

The hypertensive animal's own blood and oxygenated heparinized blood from a normal dog were perfused alternately under a constant pressure equal to the mean pressure of the dog in the femoral artery of the unoperated leg. The time required for 50 c.c. of blood to flow into the leg was measured. Four such procedures were carried out. The results are summarized in table 2. In two experiments the blood from the normal animals

TABLE II

Vasomotor Effects of Blood from Dogs with and without Hypertension Tested on Legs of Hypertensive Dogs by Means of Retrograde Perfusion

Exper. No.	Time of Flow for 50 c.c.		Time of Flow for 50 c.c.	
	Blood from Normal Dog	Number of Trials	Blood from Hypertensive Dog	Number of Trials
I	52 sec.	3	59 sec.	4
II	57 sec.	4	47 sec.	9
III	30 sec.	3	32 sec.	3
IV	46 sec.	3	42 sec.	3

flowed somewhat faster (i.e. was vasodilator) with respect to that taken from hypertensive animals. Opposite results were obtained in the other two instances. In two experiments comparisons of vasoactive properties of the blood were made on the dog's leg after severance of the nerve connections by means of a guillotine incision at the upper thigh, involving all the tissues of the leg except for the femoral artery and vein and the femur. This procedure did not alter the results.

Neither in this nor in the preceding experiment was there any consistently greater pressor activity in the blood of animals with hypertension when perfused through its own tissues as compared with blood from normal animals.

#### PRESSOR EFFECTS OF RENAL VEIN BLOOD

If a pressor substance of renal origin is responsible for the elevation of blood pressure in renal hypertension it should be present in highest concentrations in the renal vein blood. For this reason it would appear advisable

to compare the vasomotor properties of renal vein blood coming from ischemic and from normal kidneys.

Hypertension was produced in eight dogs by constricting one renal artery. After the blood pressure had risen significantly (average 32 mm. of mercury) the animals were heparinized and under nembutal anesthesia an abdominal incision was made and both renal veins cannulated. Blood from the normal and ischemic kidney was collected simultaneously, centrifuged, filtered, and the vasomotor effects of the plasma compared. The dog's tail amputated at the completion of the collection of the blood samples was used as a test object, the method being the same as that previously described for the rabbit's ear.

The blood coming from the ischemic kidney was depressor in five cases and pressor in three instances as compared with blood from the unoperated kidney of the same animal (table 3). These results agree with those of

TABLE III

Vasomotor Effects of Renal Vein Blood from the Ischemic and Unoperated Kidney of Dogs with Hypertension Due to Unilateral Renal Ischemia

Exp. No.	Elevation of Blood Pressure Following Renal Ischemia mm. mercury	Test Object	Relative Effect of the Blood from Ischemic Kidney
1	35	Hypertensive Dog's Tail	Depressor
2	45	"	Pressor
3	30	"	Depressor
4	35	"	Depressor
5	40	"	Pressor
6	35	"	Pressor
7	10	"	Depressor
8	25	Rabbit's Ear	Depressor

Collins and Hoffbauer who found no increased pressor effect of the renal vein blood of a dog with hypertension due to renal ischemia.<sup>13</sup>

#### THE LOCAL REGULATION OF BLOOD FLOW BY VESSELS OF NORMAL AND HYPERTENSIVE ANIMALS

In the following experiment it was shown that both normal and hypertensive vessels deprived of both central nervous system connections and circulating blood possess tonus and retain the ability to dilate and constrict actively.

The amputated tails of dogs with hypertension induced by constricting both renal arteries were perfused with Tyrode's solution in the manner previously described for the rabbit's ear. After the state of the vessels became constant, the inlet tube leading to the tail was clamped and the pump stopped for 10 minutes. When the perfusion was reestablished, the fluid level in the manometer tube fell rapidly, demonstrating that the vessels had

dilated. After a short while the vessels began to constrict, reaching their former state within 30 to 45 minutes (figure 4A). The same sequence of events may be observed using the tails of non-hypertensive dogs or the isolated ears of normal rabbits (figure 4B).

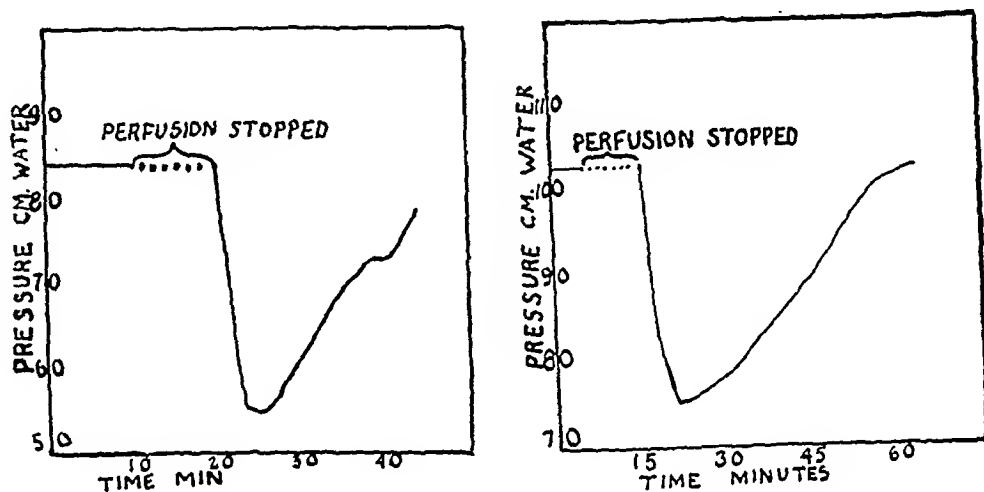


FIG. 4 A and B. Constant volume perfusion of isolated organs with Tyrode's solution. Effect on vascular tonus of stopping perfusion.

A. Perfusion of amputated rabbit's ear—perfusion stopped for 10 minutes.

B. Perfusion of amputated tail of dog with experimental renal hypertension—perfusion stopped for 10 minutes.

This reaction is undoubtedly similar to the well known phenomenon of reactive hyperemia and it has been previously shown that reactive hyperemia occurs in the denervated human hand.<sup>27</sup> In these experiments the degree of tonicity was not known and it cannot be concluded that hypertonicity was present at the onset of perfusion. They indicate, however, that local changes may be of importance in regulating vascular tonus in tissues of normal or hypertensive animals.

#### DISCUSSION

In the previous paper\* the theory was advanced that hypertension may be due to an increased humoral concentration of a pressor substance produced in the kidneys although other factors such as the integrity of the adrenal gland may play an important rôle. In support of this theory it was shown that extracts prepared from kidneys of patients and animals with hypertension had greater pressor effects than those made from normal kidneys. If this theory were correct one would expect to find an increased concentration of this substance in patients and animals with hypertension and particularly in the renal vein blood of such animals. The vasomotor effects of blood expected to contain such a hypothetical pressor substance was compared with control blood in 39 cases (table 4). In 31 instances differences between the two were noted, and in 23 of these (74 per cent) the hypertensive group was relatively depressor compared with the

\* This issue page 1604.

normal. In the three patients with acute glomerulonephritis the blood was comparatively depressor during the hypertensive phase of the disease. Following recovery, when the blood pressure declined to the normal level, the blood became pressor in two instances. These results make it unlikely that hypertension is due to directly acting vasoconstrictor substances such as epinephrine or pituitrin.

TABLE IV

Vasomotor Effects of Blood Expected to Contain a Hypothetical Pressor Substance Compared with Control Blood

Source of Blood with Hypothetical Pressor Substance	Source of Control Blood	Test Object	Action with Respect to Control Blood		
			Pressor	No Diff.	De-pressor
Plasma from patients with hypertension	Plasma from patients with normal blood pressure	Perfusion of rabbit's ear	2	5	13
Whole blood from dogs with hypertension	Whole blood from normal dogs	Perfusion of tail of hypertensive dog	1	1	3
Whole blood from dogs with hypertension	Whole blood from normal dogs	Retrograde perfusion of hypertensive dog's leg	2	0	2
Renal vein blood from ischemic kidney of dogs with hypertension	Renal vein blood from normal kidney of dog with hypertension	Perfusion of tail of hypertensive dog	3	0	5
			8	6	23

The failure to find the vasoconstrictor material may be due to one or more of the following factors.

Pickering and Prinzmetal<sup>28</sup> have recently found that renal extracts in certain circumstances may lose their pressor property and have depressor effects. Thus, the material may cause only a depressor effect when injected into rabbits anesthetized with urethane. Epinephrine and other sympathomimetic substances continued to give pressor effects under the circumstances. In this connection Friedman and Abramson<sup>29</sup> observed that renal extracts which raised blood pressure when injected into animals produced depressor effects when perfused through isolated tissues. The preparations were similar to those used in these experiments. It is possible that under the circumstances of the perfusion experiments the vessels were altered so that the renal substance in the blood caused dilatation instead of constriction. This might explain the frequent finding of depressor effects of blood in the hypertensive group.

It is also possible that the substance is not directly pressor in itself but

causes the pressor response after a local change in the vessels. The finding of persistent tonus in denervated hypertensive vessels perfused with Tyrode's solution is in favor of this suggestion. In these experiments, the perfusion was necessarily of relatively short duration. It is possible that more prolonged perfusions are necessary to cause the local change necessary for the constrictor response.

It should be pointed out that the cause of the arterial tonus that constitutes the peripheral resistance in subjects with normal blood pressure is not known. It is not nervous since completely sympathectomized animals may have normal blood pressure.<sup>30, 31</sup> It does not appear to be due to direct effect of a pressor substance in the blood since it has been shown that tonus is present in denervated vessels perfused with Tyrode's solution. Thus our knowledge of the peripheral resistance in subjects with normal blood pressure is in the same position as our knowledge of increased peripheral resistance in subjects with hypertension. It would seem probable that the hypertonus of hypertension is merely an increase of the unknown factor or factors responsible for normal tonus. Whether the kidneys and their pressor substance are concerned in the maintenance of the vascular tonus responsible for normal blood pressure as well as high blood pressure must be left for further investigation.

### CONCLUSIONS

1. Cross transfusions of large volumes of whole blood between patients with malignant hypertension and persons with normal blood pressure were performed four times. In no instance was there a significant change in blood pressure in either group of subjects.

2. Rabbits' ears were perfused with plasma taken from patients with various types of hypertension and subjects with normal blood pressure. In the majority of instances the plasma removed from hypertensive individuals was relatively depressor.

3. Plasma from a patient with adrenal pheochromocytoma collected during a paroxysm of hypertension had a marked pressor effect on the rabbit's ear preparation. Following removal of the tumor, the blood pressure returned to normal and the pressor effect of the plasma disappeared.

4. The blood from dogs with hypertension due to renal ischemia is no more pressor than that from normal dogs when perfused through the hypertensive dog's own tissues (tail or hind limb).

5. Renal vein blood from the ischemic kidney of dogs with hypertension due to unilateral renal ischemia is not more pressor than that from the unoperated kidney of the same animal when perfused through the dog's tail.

6. Tonus and the ability to dilate and constrict are present in vessels of normal and hypertensive animals deprived of both central vasomotor nervous connections and circulating blood.

7. In 31 instances differences were observed in the vasomotor effects of

blood taken from patients and animals with hypertension as compared with control blood. In 23 of these cases the hypertensive blood was relatively depressor.

The authors want to thank Drs. B. S. Oppenheimer and Harry Goldblatt for their aid and advice.

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# TROPICAL AND NONTROPICAL SPRUE (CHRONIC IDIOPATHIC STEATORRHEA): THEIR PROBABLE INTERRELATIONSHIP \*

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"For those Aphthae described to us by the ancient founders of Medicine are to us so diverse, that they differ in every climate." (Vincent Ketelaer: "De aphthis nostratibus, seu Belgarum Sprouw," 1669.)

## HISTORICAL ASPECTS

THE classic descriptions of Hillary (1759), Manson (1880) and van der Burg (1880) not only established the clinical syndrome of tropical sprue in the medical literature, but served in a sense to establish certain geographical limits within which the disease was normally confined. The original conception that sprue is found only in certain tropical and subtropical climates has been vigorously supported by authorities on tropical medicine and instances in which the syndrome was reported to have appeared elsewhere were regarded as frequently being due to diagnostic error. To quote Manson-Bahr, "One fact may be accepted as certain, that instances of genuine sprue arising *de novo* in permanent residents of temperate Europe usually are very rare and have seldom been recorded." It has of course been long since conceded by these students of the subject that the disease may develop in northern latitudes provided the affected individual formerly lived in the tropics.

The idea that sprue or a disease very closely allied to it might occur with considerable frequency in temperate climates is by no means new. Hanes<sup>10</sup> has called attention to a description of what might well have been sprue in the writings of Aretaeus (first century, A.D.), and Vincent Ketelaer's early account (1669) has been widely quoted. Neither of these descriptions is entirely satisfactory and may be considered subject to individual interpretation. Samuel Gee, who knew of the existence of tropical sprue, was the first to describe (in 1888) a syndrome resembling sprue in children and adults who had never left England. Von der Scheer (1905) noted a similar instance of sprue in a native of Holland. Herter (1908) and Heubner (1910), whose studies were concerned largely with the celiac disease of infancy, made valuable contributions to early knowledge of the physiology of "intestinal insufficiency" and thus indirectly attracted attention to the non-tropical forms of sprue.

The history of the sprue syndrome in the United States is of considerable interest. The early observations of Edwin Wood of Virginia and of Simon of New Orleans established the fact that the disease was not infrequently

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seen in natives of the southern states. Later, descriptions appeared from northern hospitals and clinics. References to these accounts and to many other earlier reports of sprue in temperate climates are included in Ashford's bibliography of sprue, which has recently been ably edited by Frederic Hanes.<sup>19</sup> These early accounts appear to have been regarded as medical curiosities and, because of the belief that sprue was essentially a tropical disease, the condition was reported under a variety of diagnoses.

In addition to these reports, a considerable number of patients with the cardinal symptoms of sprue (fatty diarrhea, glossitis, wasting and anemia, and certain metabolic and nutritional disturbances) have been encountered in temperate climates. To the condition in this group of cases the rather unfortunate term "idiopathic steatorrhea" has been given, apparently for the reason just mentioned. This condition has been regarded as occupying an intermediate position between celiac disease and tropical sprue. As more investigators interested in deficiency diseases have become interested in the problem, accounts of such cases have increased almost in geometric progression. Thaysen's monograph (1932) refers to many of the earlier reports and includes his own well-studied cases. Bennett, Hunter and Vaughan also reported a series of 15 cases in 1932; Mackie, a year later, reviewed 71 cases and added one of his own. A rather cursory examination of the literature for the last three years reveals more than 50 additional cases, from such widely scattered sources as Syria, Morocco, Turkey, Italy, Germany, Holland, France, Belgium, Great Britain, the Scandinavian countries and the northern and southern parts of the United States. Some of the more interesting<sup>20, 48, 50, 63</sup> of these recent accounts are cited in the bibliography. Much notable work on the etiology of sprue and its relation to other deficiency diseases and to pernicious anemia has appeared during this period.

Out of the various reports and studies just mentioned, two facts emerge which may be stated about as follows: (1) that tropical sprue, or at least a condition which is virtually indistinguishable from it, has been observed in many portions of the temperate zone in recent years, and (2) that another disease syndrome, differing from tropical sprue chiefly by virtue of its extreme chronicity and an associated tendency to disturbed calcium metabolism and skeletal deformities, has also been described under the heading of "idiopathic steatorrhea."

It has been suggested that this latter condition is essentially a form of celiac disease which continues into adult life and that it is not identical with sprue. Are these conditions, then, fundamentally one and the same, subject only to geographic, racial and climatic variations, or are they independent diseases? Since few have had the opportunity to study both diseases, differences of opinion naturally have arisen. Authorities on tropical medicine incline to the view that sprue and idiopathic steatorrhea are separate diseases, and in this view they are supported by certain English students of the last-named condition. Hess Thaysen<sup>63</sup> in Denmark and Hanes and McBryde in the United States believe that the conditions are identical.

## SCOPE OF PRESENT REPORT AND MATERIAL ON WHICH BASED

The present report concerns itself with "nontropical" sprue or "idiopathic steatorrhea" affecting certain residents of the United States who have been observed during the past ten years at The Mayo Clinic. This condition has been noted with increasing frequency and we now have records of 32 cases in which the presence of the sprue syndrome, with or without various accompanying metabolic disorders, was well established. The affected individuals came chiefly from the central and north central states. Our clinical material is only infrequently affected by visitors from the tropical climates, although we do see occasional instances of "imported" tropical sprue, chiefly in missionaries and physicians on leave from tropical stations.

The material to be reviewed therefore comprises three groups of cases: (1) 14 cases of sprue contracted in the tropics in which the patients were seen at various times thereafter; (2) 10 cases of sprue of nontropical origin, which cases have previously been reported and cited here chiefly because of certain interesting recent developments in these cases, and (3) 22 additional cases of nontropical sprue which have not previously been reported.

No attempt will be made to discuss the voluminous literature on tropical sprue or to describe the disease fully. It would be ridiculous to claim any large experience with it at The Mayo Clinic although the 14 such cases which have been observed here in recent years will be mentioned briefly. The details of six of these cases in which patients were seen during the active phase of the disease are recorded in table 1; the remaining eight patients had what was described as "incomplete sprue" or had been previously treated, with partial or complete success. All of the patients had developed the disease while living in regions where sprue is known to be endemic, and a number of them came to the clinic with a previous positive diagnosis. Seven of the patients were females (ranging in age from 33 to 70 years) and seven were males (whose ages varied from 25 to 66 years). There was no history of significant dietary abnormality in any case, but in each case the usual diagnostic features of glossitis, macrocytic anemia, wasting, flatulent indigestion and fatty diarrhea were, or had recently been, present. The duration of the disease was variable, and the usual tendency toward relapse and remission was noted in certain cases. In five cases effective treatment with liver extract had been begun prior to the patients' registration at the clinic and these patients were well on the road to recovery when seen. In three other cases the diagnosis had been suspected previously and some dietetic or other treatment had been given with partial benefit. In all 14 cases the effects of the disease were evidenced only by the tongue, digestive tract and blood; the chemical, metabolic and nutritional changes seen in nontropical sprue or "idiopathic steatorrhea" were conspicuous by their absence. The typical intestinal pattern as seen on roentgenologic examina-

TABLE I  
Findings in 6 Cases of Tropical Sprue

Age years, sex	Residence	Duration	Diarrhea	Glossitis	Weight lost, pounds	Pigmen- tation	Hemo- globin, erythro- cytes and leuko- cytes	Smears	Gastric acids	Serum calcium, mg. %	X-ray of small bowel	Stools	Comment
38 M	Hawaii	12 years	Moderate and inter- mittent	Grade 1	45	Diffuse (racial?)	14.7 3,900,000 6200	Hypochromic anemia	0/16*	8.8	Dilated atonic colon	Typical fatty	Responded well to high protein diet and liver by mouth. Gained 18 pounds. Diarrhea ceased.
37 F	Central America	3 months	Moderate and con- stant	Definite	30	None	11.6 3,100,000 4700	Macrocytosis	18/36	8.7	Typical dis- turbances in jejunum and ileum	Typical fatty	Marked improvement on liver ex- tract parenterally. Blood normal 8 months later. Small bowel still showed minor changes.
66 F	Puerto Rico	3 years	Intermit- tent, not severe	Definite	20	Typical	11.7 3,150,000 5700	Macrocytosis	refused		Not done	Fatty	Diagnosed sprue in Puerto Rico. Some liver extracts at long intervals with relief.
56 M	India	12 years	Intermit- tent	History only	50	None	12.1 3,400,000 4800	Macrocytosis	0/4 (with hista- mine)		Negative; in remission	Fatty (history only)	Diagnosed sprue in India. Suc- cessfully treated with diet; then re- lapse. Improved rapidly on liver extract (intramuscularly). Blood normal three months later. Neuro- logically negative.
54 M	Philip- pines	4 years	Intermit- tent and severe	Atrophic tongue	23	None	7.1 1,570,000 3900	Macrocytic anemia, Vol. index 1.1	84/76 (with hista- mine)	8.0	Not done	Fatty (history only)	No response to extralin but prompt improvement on liver extract (in- tramuscularly). Well 2½ years later. Neurologically negative.
25 M	Nicaragua	15 months	Constant and severe	History only	23	None	9.0 2,120,000 6000	Macrocytosis Vol. index 1.2	22/38		Not done	Fatty	Excellent response to liver extract by mouth. Reticulocytes rose to 11%. Neurologically negative.

\* 0 = free HCl, 16 = total acidity.

tion was noted in certain cases. Treatment with liver extract was effective in each of these cases, the results being in some instances quite comparable to those noted in pernicious anemia.

### NONTROPICAL SPRUE

To avoid confusion in the discussion to follow, some arbitrary definition of terms will be attempted here: The "sprue syndrome" as used hereafter will refer to the disease picture mentioned in the previous paragraphs without reference to its geographic origin; "nontropical sprue" will refer to the same syndrome as seen in natives of temperate climates without reference to the development of any complicating nutritional or metabolic disorders. "Idiopathic steatorrhea" will be used synonymously with "nontropical sprue."

#### TEN CASES OF NONTROPICAL SPRUE PREVIOUSLY REPORTED

The essential clinical data in this group of cases are recorded in tables 2 and 3 (Cases 1 to 10, inclusive). Nine of these patients were residents of the North Central States; one was from Texas. Two of the patients had been born in Northern Europe but had spent their entire adult lives in the United States. Five were women, five were men. Their ages varied from 26 to 51 years, and the duration of symptoms varied from nine months to 30 years. The presenting symptoms in this group of cases included weakness, diarrhea, abdominal cramps, flatulent indigestion, and diarrhea of variable severity. Among the striking physical findings were evidence of extreme loss of weight and of muscular wasting, glossitis with local areas of atrophy of the tongue, abdominal distention, deformities of the skeleton, stunted growth, peripheral edema and tetany. It may be mentioned here that Cases 1, 2, 4, and 8 which were reported separately at an earlier date, have been reviewed and commented on by various authorities on so-called idiopathic steatorrhea and have been regarded as acceptable examples of the condition. To see these cases in their proper relation to the picture as a whole it is necessary to turn to the more recently studied group of 22 cases, the details of which are likewise found in tables 2 and 3 (Cases 11 to 32, inclusive), and to consider the subsequent developments in certain of these earlier cases.

#### ENTIRE SERIES OF THIRTY-TWO CASES OF NONTROPICAL SPRUE

To attempt to give a clinical picture of the series as a whole requires a general consideration of the symptoms and signs of the disease, since it is only in this manner that the "irregularly progressive" character of the condition, as noted by Ashford, can be appreciated. As Castle and his associates have also noted, tropical sprue does not present a static, but a dynamic, condition and this statement applies with equal force to the disease as seen in nontropical climates.

TABLE II  
Clinical Findings in 32 Cases of Nontropical Sprue

Case	Age in years, and sex	Duration	Diarrhea	Infantilism	Edema	Bony deformity	Tetany, active or latent	Glossitis	Weight lost, pounds	Amenorrhea present	Pigmentation	X-ray findings	Comment
1	31 F	Lifelong; worse last 7 years	Episodic; grade 2-3	Grade 2	None	Rachitic stigmata	Active, grade 3	Slight	45	+	Definite	None	Living and well. High protein diet and calcium, viosterol.
2	33 F	Lifelong; worst last 6 to 7 years	Episodic; lifelong	Grade 1	None	Marked osteomalacia	Active, grade 2	None	40	+	Definite eruption resembling pellagra	None	Died. No benefit from diet, calcium.
3	51 F	20 years plus	2-3 yrs. moderate	Grade 1	None	None	Active, grade 4 +	None	20	Menopause	Slight; urticaria	None	No benefit from treatment (no recent record).
4	47 F	20 years	Episodic; 20 years	Grade 2	Grade 2	None	Seasonal; active at times for 20 years	Grade 1	25	+	Slight	Jejunitis	Effectively treated. Living and well (see appendix A).
5	47 M	10 years plus	Episodic; 10 years	None	Grade 2	None	Active for 10 years	Grade 1	50		Slight	Jejunitis	Living and well. Liver extract by mouth with benefit.
6	44 M	9 years	1 year; grade 3	None	Grade 1	None	None	Grade 1	26		None	Jejunitis	No benefit from treatment (no recent record).
7	45 F	15 months	Grade 3	? small frail type	Grade 2	None	Latent; one active attack	Grade 1	22	+	None; marked pruritus	Jejunitis and ileitis	Died; hemorrhagic diathesis. Prothrombin deficiency?
8	26 M	10 years	Grade 1 to 2	Grade 2	Grade 1	Rachitic stigmata; osteoporosis	None	Grade 1	20		Slight	Jejunitis and ileitis	At first marked benefit from parenteral liver extract; later this was ineffective. Died of exhaustion.
9	47 M	6 years	Occasional severe episodes, grade 1 to 2	None	Grade 1	None	None	Grade 1	70		Eczema of hands	Jejunitis and ileitis	Indifferent response to treatment. Died at home; cause unknown.
10	44 M	12 years	Slight; irregular	None	Grade 1	None	None	Slight	18		Extensive, brownish	Ileitis slight	Good response to liver treatment.

TABLE II (continued)  
Clinical Findings in 32 Cases of Nontropical Sprue

Case	Age in years, and sex	Duration	Diarrhea	Edema	Tetany, active or latent	Glossitis	Weight lost, pounds	Amenorrhea	Pigmentation	Blood pressure	Comment
11	56 M	4 months	Grade 2+	None	None	Grade 2	30+		None	122/75	Retiucytes rose to 5.1% on liver extract. Blood normal 5 months later. Gained 20 pounds.
12	49 M	5+ years	Grade 2+ (intermittent)	None	None	Grade 1 (mild)	25+		Slight, yellowish	108/80	Liver extract given intramuscularly; gained 40 pounds. RBC normal 1 year later.
13	32 M	6 years	Grade 2 (intermittent)	None	None	Grade 1	30+		Diffuse, yellowish	110/70	No benefit from jeculin but immediate response to liver extract (intramuscularly); gained 25 pounds. Well after 4 years.
14	60 M	9 months	Grade 2	Grade 2	None	Grade 1	32+		None	110/70	Retiucytes rose to 10%. RBC up 21 million; liver extract parenterally. Rapid improvement. Diarrhea controlled.
15	23 F	2 years	Grade 3	Previously	None	Grade 1	24+	+	Slight, diffuse	84/52	Considerable liver extract with slight improvement, but reticulocyte rise did not exceed 4%.
16	44 M	3 years+	Grade 3	Definite	None	?	53+		Slight, diffuse	95/60	Never been well. Little or no effect from adequate liver. Diarrhea not controlled. Blood slightly improved. Died later at home. Marked bony deformity.
17	38 F	2 years	Grade 2	None	None	Atrophic tongue	10+	No	Diffuse melanosis, grade 3	116/70	No response to provocative test for Addison's disease. CNS negative. Marked improvement on liver extract; gained 10 pounds.
18	63 F	6 years	Moderate (intermittent)	None	None	Atrophic tongue	Indeterminate, regained on treatment	No	None	130/85	Sore tongue, anemina and diarrhea. Responded to liver extract. Relapse twice followed its discontinuance. Felt fairly well when last examined.
19	26 M	5 years	Grade 2	None	None	Not marked	27		Diffuse pigmented eruption on legs	102/74	Retiucytes rose to 11% and marked improvement in small bowel occurred on 20 day period on liver extract. Relapse followed discontinuance of treatment here.
20	37 M	13 years	Grade 2+ (intermittent)	None	None	Marked with aphthous stomatitis	18		Slight?	120/85	Under observation here for 13 years. Previously benefited by sprue diet. Improved on liver extract. RBC up to 5,000,000.
21	17 M	1+ years	Variable; never severe	Grade 2	None	Grade 1	20		Diffuse, brownish	110/60	Good response to liver extract and vitamin concentrates. Doubled weight in two years.

TABLE II (continued)  
Clinical Findings in 32 Cases of Nontropical Sprue

Case	Age in years, and sex	Duration	Diarrhea	Edema	Tetany, active or latent	Glossitis	Weight lost, pounds	Amenorrhea	Pigmentation	Blood pressure	Comment
22	30 M	4 years	Grade 3+	None	None	Grade 3	43		None	102/82	Good response to liver, but apparently discontinued treatment. Died of exhaustion and complicating mastoiditis.
23	56 M	1+ year	Grade 3	Grade 2+	None	Marked	26		Marked	90/56	Fatty stools and severe glossitis indicated sprue. Good immediate response to liver, but discontinued it and died two years later in relapse.
24*	41 M	3+ years	Grade 3	None	History of previous attack	Grade 1	30		Grade 2	92/56	Liver by mouth inadequate response, good response extract intramuscularly (practically well 5 months later). Roentgen-ray of small bowel showed improvement.
25	41 M	4 years	Grade 3	Slight, variable	Latent	Grade 3	69		None	100/60	Improved on liver extract. Still has some bone pains (osteoporosis?).
26	37 M	3 years	Grade 2+	None	None	Grade 2	21		None	105/70	Good response to liver intramuscularly. Blood normal 8 months later. Still has diarrhea at times.
27	50 M	3 years	Grade 2	None	None	Marked	17		None	120/78	Indifferent response to vigorous liver treatment. Blood improved only slightly. Patient seemed to be slowly failing.
28	53 M	1 year	Grade 2	None	None	Grade 1	20		Slight	104/60	Indifferent response to vigorous liver treatment but later definite improvement. Mild relapse 18 months later although still taking liver.
29†	29 F	4 years	Grade 3	None	None	Grade 1	23	+	Diffuse yellowish	96/76	Some liver extract (not enough) without benefit. Complicating t. b. lymphadenitis. Died. Necropsy.†
30	54 M	3½ years	Grade 2+	Grade 2	Active at times	Very slight	10		None	90/56	Improved on liver extract but bowel did not clear up entirely. Excess fat in stools at various times. Sudden death from Landry's paralysis. Blood normal before death. Necropsy.
31	49 M	20+ years	Intermittent	None	None	None	Variable		Slight	106/76	Always had irritable intestinal tract. Remarkable general improvement on liver extract intramuscularly with restoration of blood.
32	71 F	10+ months	Grade 3	None	None	Slight	37	No	Definite	90/70	Liver extract and transfusions failed to control. Blood concentration before death. Diarrhea continued. Died of exhaustion.

\* See appendix B.

† Case reported in detail by Bagen and Mendez Ferreira.<sup>43</sup>



TABLE III  
Laboratory Findings in 32 Cases of Nontropical Sprue

Case	Hemo- globin*	Erythro- cytes	Leuko- cytes	Erythrocytes, morphology	Gastric acidity		Stools	Serum calcium, mg. per 100 c.c.	Serum phosphorus, mg. per 100 c.c.	Serum bilirubin, mg. per 100 c.c.	Serum protein, gm. per 100 c.c.	Plasma cholesterol, mg. per 100 c.c.
					Free HCl	Total						
1	54	3,620,000	6,800	Macrocytic anemia	40	56	Oil or fat in excess	6.3 to 11.3	4.4 to 6.6			
2	54	3,370,000	2,700	Not examined; vol. index 0.88	18	38	Oil or fat in excess	6.3 to 8.2	2.3 to 4.5			
3	56	3,420,000	11,000	Vol. index 1.03	20	32	Fatty	1.9 to 7.7	2.4 to 4.6			
4	38	3,710,000	4,900	Hypochromasia	40	62	Oil or fat in excess	6.3 to 11.6	4.0 to 1.1		4.1 to 5.0	139
5	64	4,000,000	6,500	Hypochromic anemia	42	56	Oil or fat in excess	6.8 to 8.6	2.9 to 3.9		4.1 to 5.3	
6	64	3,250,000	5,100	Macrocytic anemia	58	64	Oil or fat in excess	8.0 to 10.5	2.2 to 3.4			103
7	67	7,790,000	5,600	Macrocytic anemia	46	58	Fat in excess	6.8 to 9.0	2.8 to 3.0		4.8 to 6.1	
8	62	2,580,000	2,700	Macrocytic anemia	22	38	Fat in excess	7.8 to 8.7	3.5 to 4.9	1.1 to 1.3	4.9†	93
9	50	2,850,000	2,300	Hypochromasia; eosinophilia	36	46	Fat in excess	8.5 to 10.4	3.6 to 1.2	1.0	5.6 to 5.9	
10	70	3,510,000	3,100	Macrocytic anemia	38	50	No fat in excess with low fat diet	9.5	1.2		7.3	

TABLE III (continued)  
Laboratory Findings in 32 Cases of Nontropical Sprue

Case	Residence	Hemoglobin, erythrocytes, leukocytes	Erythrocytes, morphology	Gastric acidity		Stools	Serum calcium average †	Serum phos- phate average †	Serum bilirubin average †	Serum protein aver- age §	Plasma cholesterol average †	Basal metabolic rate	Roentgen-ray		Miscellaneous data
				Free HCl	Total								Bowel	Bones	
11	Tennessee	13.6 2,780,000 7500	Macrocytic anemia	56	64	Fatty	9.1	4.7	1.2 (ind.)		141		Diffuse ileitis	Neg.	CNS negative.
12	Missouri	10.2 2,600,000 4700	Macrocytic anemia			Fatty	7.9	2.7	1.0				Small bowel not examined. Colon neg.	Neg.	
13	Iowa	11.7 2,680,000 3200	Marked varia- tion in size and shape; vol. index 1.15.	0 (with histamine)	6	History of fatty stools								Neg.	CNS negative.
14	Tennessee	10.7 2,290,000 5900	Macrocytic anemia	22	30	Described as fatty				5.4			Typical changes	Neg.	
15	Missouri	9.5 3,690,000 6000	Macrocytosis	0 (Ewald)	4	Variable; fatty at times. Ate very little	6.9	2.3		5.4	82		Typical changes	Osteo- porosis	Purpuric eruption at times, relieved by transfusion.
16	Montana	5.5 2,950,000 5000	Indeterminate hypochro- miasia	0 (Ewald)	20	Variable; fatty at times. Ate very little	7.9	3.9	1.0	3.5	87		Typical diffuse in- volvement	Osteo- porosis, grade 3. Scoliosis	Died.

TABLE III (continued)  
Laboratory Findings in 32 Cases of Nontropical Sprue

Case	Residence	Hemoglobin, erythrocytes, leukocytes	Erythrocytes, morphology	Gastric acidity		Stools	Serum calcium average†	Serum phos- phate average†	Serum bilirubin average†	Serum protein average‡	Plasma cholesterol average†	Basal meta- bolic rate	Roentgen-ray		Miscellaneous data
				Free HCl	To- tal								Bowel	Bones	
17	South Dakota	8.0 3,850,000 3500	Macrocytes and hypo- chromasia	26	46	Variable; had been fatty	8.7		1.2	6.6			Diffuse changes	Slight osteo- porosis	Melanotic pigmen- tation. Joint pains.
18	Kentucky	14.4 4,870,000 9200	Occasional macrocyte	14	40	History of fatty stools. Normal when ex- amined	9.9			7.4		-7	Normal	Negative	Prothrombin 47% normal.
19	Kentucky	11.1 2,440,000 6000	Macrocytic anemia	58	64	Very fatty	9.0	2.8		7.8	119		Typical changes	Osteo- porosis	Pigmented skin le- sions on legs. Sub- acute combined de- generation.
20	Texas	9.3 2,470,000 10,800	Macrocytic anemia	12	22	Fatty	8.8						Typical changes		
21	Michigan	10.8 2,690,000 3000	Macrocytic anemia	42	60	Fatty	9.5		3.1		104			?	History of bone pains and green- stick fracture.
22	Missouri	13.6 4,350,000 9700	Hypochro- masia	0 (with histamine)		Described as volumi- nous and fatty	9.3		1.2					?	
23	Wisconsin	9.2 1,890,000 4400	Macrocytic anemia			Fatty									

\* Hemoglobin in gm. per 100 c.c.; erythrocytes and leukocytes per cubic millimeter of blood.

† See text. Case previously studied by Weir and Adams.

‡ Milligrams per 100 c.c.

§ Grams per 100 c.c.

TABLE III (continued)  
Laboratory Findings in 32 Cases of Nontropical Sprue

Case	Residence	Hemoglobin, erythrocytes, leukocytes	Erythrocytes, morphology	Gastric acidity		Stools	Serum calcium average†	Serum phos- phate average†	Serum bilirubin average†	Serum protein average‡	Plasma cholesterol average†	Basal meta- bolic rate	Roentgen-ray		Miscellaneous data
				Free HCl	Total								Bowel	Bones	
24	Minnesota	6.6 2,800,000 9600	Macrocytic anemia	40	54	Fatty	8.9			6.3	150	+11	Typical changes	Osteo- porosis	
25	Illinois	14.1 3,980,000 5100	Macrocytosis	8	16	Fatty	5.3	1.3		5.5			Diffuse enteritis		Peripheral neuritis. (Crossed leg palsy?)
26	Alabama	11.1 2,800,000 5800	Macrocytic anemia	6	12	Had been fatty						-6			
27	Illinois	11.4 3,600,000 8900	Macrocytic anemia	68	70	Fatty	8.8	3.3					Typical changes		Normal enzymatic activity in duo- denal contents.
28	Kansas	14.5 3,640,000 6100	Macrocytic anemia	0 (with histamine)		Fatty	7.6	2.7		6.3			Typical changes	Slight osteop- orosis	Normal enzymatic activity in duo- denal contents.
29	Wisconsin	11.1 3,590,000 16,000	Macrocytosis	0 (with histamine)		Fatty	7.6			4.2	92		Typical changes		Normal enzymatic activity in duo- denal contents.
30		15.4 4,360,000 5600	Some persis- tent macro- cytosis	0 (with histamine)		Fatty	7.9	3.0	1.0 (ind.)	5.2	158		Typical changes		Sprue diet + cal- cium therapy prior to admission.
31	†	12.5 2,790,000 4500	Macrocytic anemia	36	40	Fatty at times	9.3		1.2	5.1 (rose to 7.1 in 60 days)	145		Normal		Normal enzymatic activity in duo- denal contents.
32	Kansas	14.1 3,650,000 9600	Macrocytosis	0 (with histamine)		Voluminous and fatty at times	7.9						X-ray not satis- factory		

|| Marine engineer, but has not been in tropics in past 10 years.

† Had lived in China but had symptoms of sprue before going there.

*Symptoms.* All of the 32 cases of nontropical sprue of this series have certain features in common, although not all of these symptoms were present in every case at each individual period of study. These common features are glossitis and stomatitis, emaciation, fatty diarrhea, various types of anemia, disturbances of the metabolism of calcium and of protein, and a group of symptoms related to various vitamin deficiencies. These will be discussed in detail in later paragraphs.

There are no definite prodromal symptoms of nontropical sprue, although certain patients who later had the full-blown disease gave a history of chronic remittent gastrointestinal disturbances, nausea, vomiting, anorexia, intolerance to food, and intestinal irritability. In spite of these complaints it was difficult or impossible to uncover a history of dietary errors in most of these cases and, in fact, with one or two exceptions a normal mixed diet had been taken more or less regularly up to the time symptoms appeared. As will be noted from tables 2 and 3, the course of the disease was extremely chronic and a majority of the patients were seen three or more years after the onset of the earliest definite symptom, usually diarrhea. Remissions and relapses punctuated the progress of the disease in most instances thereafter. Nausea and vomiting, or what had been taken to be an infectious gastroenteritis, were frequently mentioned as an early complaint. Diarrhea, at first intermittent and later more or less continuous, was the next common development. Stools were often described as brown, watery and offensive at the onset; later, voluminous, foul, yellow-gray, fatty stools were noted. As the diarrhea became more severe, abdominal cramps and flatulent dyspepsia became increasingly troublesome. Loss of weight and weakness were usually progressive and extreme. Glossitis and stomatitis of such severity as to produce definite symptoms were described by 24 of the 32 patients. The oral lesions were not always continuously present and were not necessarily active at the time of examination. Pallor and cutaneous pigmentation were occasionally mentioned. More than half the patients complained of bone and joint pains, which in many cases was an early and annoying symptom. Amenorrhea was noted by six of the seven female patients between the ages of 18 and 45 years. Tetany, which was almost invariably related to exacerbations of the diarrhea, was noted by nine patients and dependent edema was a rather conspicuous feature of the disease in 11 cases.

*Physical Examination.* Physical examination revealed as its most striking finding a remarkable degree of malnutrition with muscular wasting and cachexia. Losses of 30 pounds (13.5 kg.) or more were extremely common. Many of the patients had a peculiar mummy-like appearance with definite, diffuse, yellowish-brown pigmentation of the skin (figure 1). Lack-luster hair, club fingers and brittle nails were common; a distended and flatulent abdomen was almost an invariable finding. The appearance of the tongue and mouth varied considerably. Moderate atrophy with redness of the tip and edges of the tongue was most commonly seen, but in

certain cases diffuse stomatitis or definite aphthous lesions of the tongue and mouth were noted.

In addition to these signs, certain nutritional disturbances and deficiency syndromes were observed as complications of the original disease. Pellagrous skin eruptions were noted in two cases (figure 2). In other cases an itching, pigmentary dermatitis of patchy distribution developed. Petechial hemorrhages were observed in two cases. Edema was noted in 11 cases; it was usually confined to the lower extremities and in only one case did ascites develop (Case 8). Infantilism, bony deformities (including scoliosis, knock-knee and rachitic stigmas) and stunting of growth were

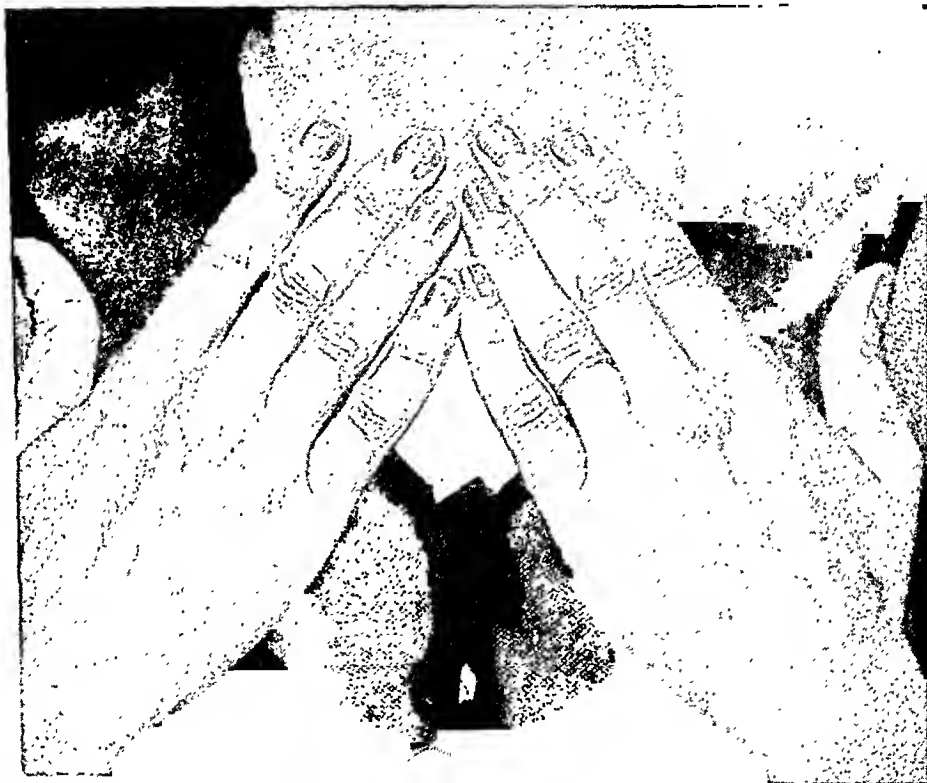


FIG. 1. Melanotic pigmentation of the skin in sprue. In this case the presence of Addison's disease was excluded by metabolic studies performed during a period of salt deprivation.

noted in five cases, and osteoporosis was seen in these and in four additional cases. In three cases a diagnosis of subacute combined degeneration of the spinal cord was made by consulting neurologists. One patient had a transient polyneuritis associated with pellagra. Nine patients had definitely positive Chvostek's and Trousseau's signs at the time of examination. Cataracts, which have been mentioned by other writers, were not seen in this series of cases, but a slit-lamp examination was not routinely carried out. Some of the significant "complications" are given in table 4; their nature will be discussed later.

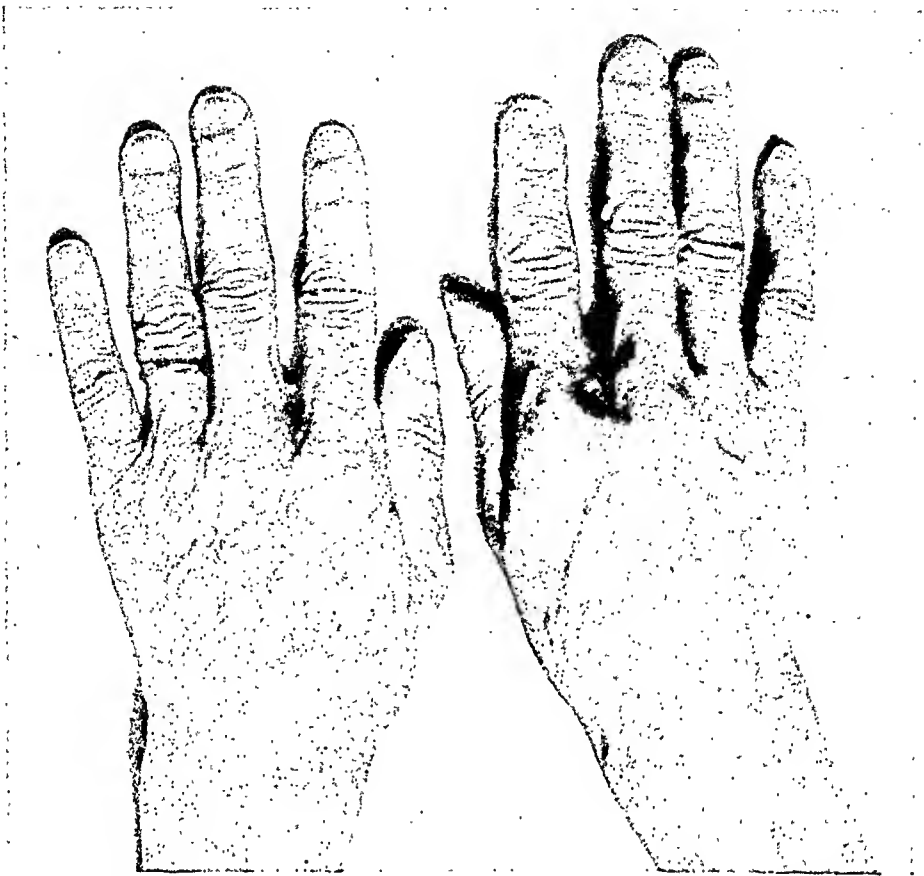


FIG. 2. Subsiding pellagrous dermatitis (see Case 4 in appendix).

TABLE IV  
"Complications" or Late Sequelae of the Sprue Syndrome

Complication	Number of cases
Infantilism . . . . .	4
Bony deformities or fractures . . . . .	4
Osteoporosis . . . . .	9
Tetany . . . . .	9
Amenorrhea . . . . .	6
Edema (hypoproteinemia) . . . . .	11
Hemorrhagic features . . . . .	2
Subacute combined degeneration . . . . .	3
Polyneuritis (pellagra) . . . . .	1

*Vitamin Deficiencies.* As mentioned in an earlier paragraph, one of the significant features of sprue as seen in temperate climates is the multiplicity of vitamin deficiencies which may develop, presumably because of failure of absorption of these substances in the digestive tract. For obvious reasons the fat-soluble protective substances are most likely to be affected. A deficiency in the absorption of vitamin A, as shown by night blindness and xerosis conjunctivae, has been described (Riddell). Malabsorption of

vitamin D may be inferred from the calcium deficiencies previously mentioned and the development of osteoporosis, osteomalacia and tetany. Linder and Harris showed that the administration of vitamin D alone was of considerable clinical value, an observation which has been fully confirmed by others. No data are available on the utilization of vitamin E. One of our patients (Case 1) went through a normal pregnancy after the steatorrhea and calcium deficiency had been brought under control. The absorption of the most recently discovered fat-soluble vitamin, vitamin K, may conceivably be adversely affected by any type of sprue. A hemorrhagic diathesis has been described in connection with tropical sprue, and one of our patients (Case 7) died at home in a manner strongly suggestive of prothrombin deficiency. In one other case recently observed the normal prothrombin content of the plasma was reduced by more than 50 per cent. Further studies on vitamin K absorption in cases of sprue may lead to elucidation of the curious hemorrhagic state which may cause a fatal termination of the disease.

Data on the absorption of the water soluble vitamins are by no means complete. The antineuritic vitamin (vitamin B<sub>1</sub>) is absorbed at least to the point where peripheral neuritis is prevented in the majority of cases. The daily requirements of the vitamin are, however, obviously increased by the diarrhea. The pellagra-preventing factor may be poorly assimilated in certain cases, as indicated by our two patients with pellagrous skin lesions (Cases 2 and 4). The absorption of other factors in the vitamin B complex has not as yet been thoroughly studied but, as Castle and Rhoads and their associates suggested, a failure of utilization may be intimately and fundamentally concerned with the etiology of the disease. Little information is available as to the absorption and utilization of vitamin C. We have studied the concentration of this material in blood and urine in a few cases and obtained results which fell within the limits of normal.

It should again be emphasized at this point that one of the significant differences between tropical and nontropical sprue has to do with the number and variety of avitaminoses which have been reported in the latter condition. The recently reported case of Fullerton and Innes is an excellent example of this phenomenon.

*Laboratory Data.* Stools. No better description of the typical stools in sprue can be offered than that of Samuel Gee: "Signs of the disease are yielded by the feces; being loose, not formed, but not watery; more bulky than the food taken would seem to account for; pale in colour, as if devoid of bile; yeasty, frothy, an appearance probably due to fermentation; stinking, the stench often very great, the food having undergone putrefaction rather than concoction." It should not be inferred that all stools are of this kind in either tropical or nontropical sprue or that diarrhea is a constant and invariable symptom. At various times fairly normal or even constipated stools may be passed whereas, at other times, a watery diarrhea is temporarily conspicuous.



The stools in this series of 32 cases of nontropical sprue yielded large amounts of fat on analysis, but the degree of steatorrhea varied considerably with the stage of the disease and the patient's diet. Many of the patients observed at the clinic had learned to restrict their intake of fat which of course tended to control the diarrhea and alter the chemical composition of the stools. Chemical examination of the stools was not carried out routinely in this series of cases and the diagnosis of steatorrhea was based in many instances on microscopic examination of specimens stained for fat. The degree of loss of fat was obviously variable, but in many specimens 30 per cent or more of the dried stool consisted of fat. Thaysen's<sup>62</sup> patients, who were on a high fat diet, lost from 13 to 27 per cent of the fat ingested; most of the chemical analyses made in cases in this series fell within this range. The patient in Case 8, whose fat tolerance was studied by Weir and Adams and who was on a fat intake of 45 gm. per day, lost approximately one-third of this amount in the stools. The patient previously reported from the clinic (Case 29) by Mendez Ferreira and Borgen, excreted 62 gm. of fat in one day on an intake of 65 gm. In some of our earlier cases the tolerance to fat in the diet was low, not exceeding 40 to 50 gm. daily. Stools contained chiefly split or neutralized fat, a finding which has been reported by many other observers.

**Blood.** Three types of anemia have been described in nontropical sprue: (1) a hypochromic or secondary form; (2) a hyperchromic, macrocytic type, in which the morphologic features of the formed elements of the blood are almost identical with those seen in pernicious anemia, and (3) an erythroblastic type. As Thaysen and others have mentioned,<sup>29, 30, 48, 62</sup> the hematologic picture is not necessarily constant in any given case, being modified by the course of the disease and by treatment. In our earlier group reported from the clinic<sup>58</sup> (Cases 1 to 10, tables 2 and 3) half of the 10 patients had a typical macrocytic anemia. In the second group (Cases 11 to 32) 17 of the 22 patients showed a similar picture. Four patients had a moderate to marked hypochromasia, with variations in the size, shape and staining properties of the erythrocytes. In one other case (Case 30) the stained smears of the blood showed many nucleated red cells and Howell-Jolly bodies, a finding which was explained by the extreme atrophy and fibrosis of the spleen at necropsy. It is interesting to compare the hematologic findings in our series of cases (table 5) with the report of Fairley

TABLE V  
Blood Findings and Gastric Acidity

	Old series (10 cases)	New series (22 cases)
Average hemoglobin (gm. per 100 c.c.)....	9.6	10.2
Erythrocyte count (millions per cu. mm.)..	3.41	3.3
Achylia (6 cases checked with histamine)....	0	8
Macrocytic hyperchromic anemia.....	5	17 cases
Hypochromic anemia.....	5	5 cases

and his colleagues<sup>14</sup> on the blood in tropical sprue. The average values for hemoglobin and erythrocyte counts are almost identical. Abnormal levels of bilirubin in the blood were not noted in this series of cases. Leukocytosis was rare except in the presence of complications.

We did not have an opportunity to perform biopsies of the bone marrow in any case of this series. These have been described in sprue by others (Castle and associates<sup>10</sup>), however, and Thaysen,<sup>22</sup> in studying nontropical sprue, has noted a red bone marrow with megaloblastic regeneration. In the late stages of the disease a hypoplastic bone marrow has been encountered.

**Gastric acidity.** Free hydrochloric acid was demonstrated at one time or another in all of the 10 cases previously reported (Cases 1 to 10), although it was often necessary to use histamine as a stimulant to demonstrate it. In the second series of 22 cases (Cases 11 to 32), eight patients had a lack of hydrochloric acid at the time of examination; in six of these cases the finding persisted after stimulation with histamine. Two patients refused gastric analysis. These figures correspond roughly with those of Castle and Rhoads and their associates<sup>10</sup> who found anacidity in about 30 per cent of their cases of tropical sprue. Because of the possibility of pancreatic dysfunction in certain of our cases, the duodenal content was studied for enzymatic activity in six cases. In each case normal values for lipase, trypsin and amylase were found.

**Calcium and Phosphorus Metabolism.** The relatively high incidence of tetany, osteoporosis and skeletal deformity has already been mentioned. These conditions obviously depend on long-continued losses of calcium from the organism. It has been shown by Marble and Bauer that a positive calcium balance can be obtained in the presence of steatorrhea with a high intake of calcium, whereas with a low intake of calcium a negative balance prevails. Diarrhea increases fecal calcium losses, as might be expected, the urinary excretion of calcium remaining unchanged.

Roentgenologic examination of various bones was carried out in a number of cases and, in nine, definite osteoporosis was demonstrated. The two patients who showed the most striking skeletal defects (Cases 2 and 16) both had marked scoliosis and kyphosis of the degree one might expect to see in osteomalacia (figure 3). Roentgenologic studies of the bones of these patients showed osteoporosis, deformities of the pelvis and long bones, and pseudofractures ("umbauzonen").

As Fairley and others<sup>11</sup> have noted in tropical sprue, slight reductions in the blood calcium (1 to 1.5 mg. per 100 c.c.) were common. Such slight abnormalities were noted in 19 cases in our series whereas, in nine other cases with latent or active tetany, the average level of blood calcium was approximately 6 mg. per 100 c.c. The serum phosphorus was always lowered in this group of cases, thus differentiating this form of tetany from that of parathyroid insufficiency. Phosphatase activity of the serum was within normal limits in the few cases studied.

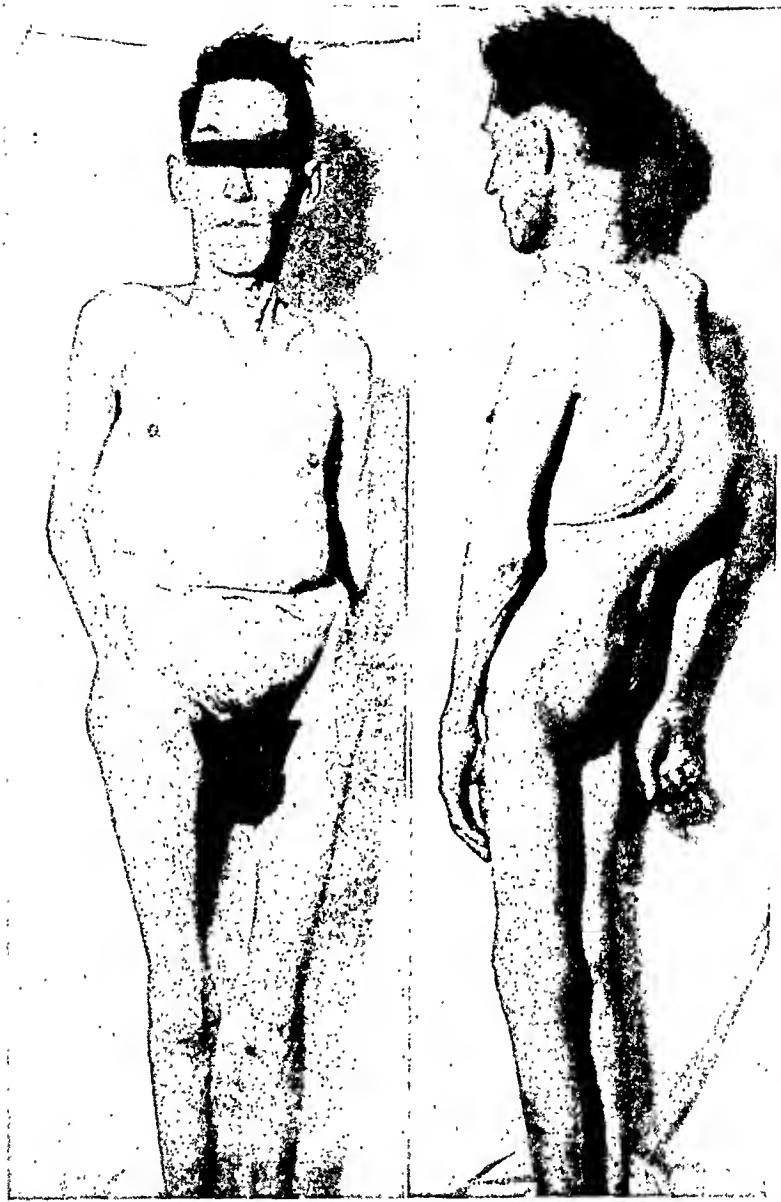


FIG. 3. Skeletal osteoporosis and associated skeletal deformities in untreated sprue (Case 16).

*Chemical and Metabolic Disturbances.* A flat blood sugar curve after the oral administration of glucose has been described in cases of nontropical sprue by Thaysen<sup>62</sup> and Hansen<sup>21, 22</sup> and in native tropical sprue by Fairley.<sup>11</sup> We have noted abnormal glucose tolerance curves of this type in five of our cases of nontropical sprue (figure 4); a normal curve was found in one other case in which the patient was under treatment. Thaysen<sup>62</sup> noted that a normal hyperglycemia was the rule if glucose was given intravenously or if epinephrine was administered to patients with tropical sprue, and he argued from these observations that some endocrine disturbance must be postulated in order to explain this seeming contradiction

in carbohydrate metabolism. Fairley<sup>11</sup> and others felt that decreased absorption from the intestine explained the lack of alimentary response, while a failure of insulin production incident to starvation might account for the hyperglycemia when glucose was given by vein. The relation of the absorption of vitamin B<sub>1</sub> to these disturbances in carbohydrate metabolism has not been investigated.

In our series of cases of nontropical sprue a reduction in the blood cholesterol proportionate to the severity of the steatorrhea was commonly observed. Fairley<sup>11</sup> previously noted a similar effect in tropical sprue. Barker and Rhoads have recently demonstrated an absence of the usual rise in blood lipids after a fat meal in cases of sprue, indicating failure of intestinal absorption. This abnormality was corrected following the administration of liver extract. This malabsorption of fat is, of course, the

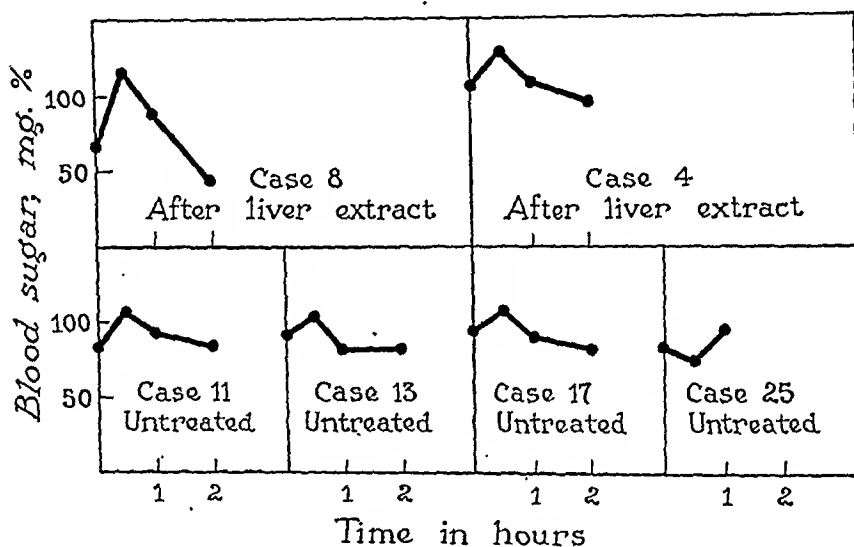


FIG. 4. Glucose tolerance curves in sprue.

most obvious explanation of the phenomenon of steatorrhea, but other investigators, notably Bauer and Moncrieff and Payne, have suggested an active elaboration and excretion of fat from the bowel.

Little is known about nitrogenous metabolism in sprue, but it has been noted that moderate azotorrhea may occur. This is considerably less than that noted in pancreatogenous steatorrhea, a fact which may distinguish the two conditions. One patient (Case 8) was barely in nitrogen balance during one attack of diarrhea but stored nitrogen while under treatment later. It seems probable that some losses of nitrogen must occur through the stools and that, in addition, there may be deficient absorption of protein and protein-forming substances from the intestinal tract of these patients. As previously mentioned, 11 of our 32 patients had edema which was associated with a low serum protein and a normal or reversed albumin-globulin ratio. In 18 cases in which the serum protein was determined, the range was from

4.1 to 7.8 gm. per 100 c.c., or an average of 5.5 gm. Fairley's<sup>11</sup> figures for tropical sprue were somewhat higher (table 6).

It is interesting to note that an elevated metabolic rate has been regarded as a diagnostic feature of nontropical sprue (Thaysen,<sup>62</sup> Hansen<sup>21, 22</sup>). How reliable this is may be questioned, since starvation alone may elevate the rate. My own data are not sufficient to warrant an opinion on the point.

*Roentgenographic Studies of the Intestinal Tract.* The one explanation which would serve to include all the various reported disturbances in the metabolism of carbohydrates, proteins, fats and calcium in the sprue syndrome is, as has been mentioned previously, failure of absorption from the intestinal tract. The idea of intestinal dysfunction in sprue is by no means new, and it has received some support from pathologic observations as well as from recently reported roentgenologic studies of the small bowel. Such studies have been reported by Camp and me, by Mackie and his cowork-

TABLE VI  
Blood Chemical Data

	Cases	Reading per 100 c.c.
Serum bilirubin . . . . .	10	1.5 mg. or less
Blood cholesterol . . . . .	13	82-158 mg. (range)
		123 mg. (average)
Serum proteins . . . . .	18	4.1-7.8 gm. (range)
		5.54 gm. (average)
Serum calcium . . . . .	9*	4.9-6.9 mg. (range)
		6.13 mg. (average)
	19**	7.6-10.0 mg. (range)
		8.7 mg. (average)

\* Patients with active or latent tetany.

\*\* Other patients.

ers,<sup>38, 39</sup> and by Miller and Barker. The characteristic picture is that of delayed motility and alteration in the mucosal relief of the small intestine, especially the jejunum; the contour of the lumen of the bowel is smoothed out, the usual markings of the valvulae conniventes are obliterated and the barium is clumped in elongated masses (figure 5). Dilatation of the colon and loss of its usual haustral markings are often conspicuous. Not enough other deficiency diseases have been studied roentgenologically in this manner to warrant any conclusions as to the specificity of these findings; Camp has noted a similar appearance in the case of a pellagrous patient and in that of a child with celiac disease. Pancreatogenous diarrhea has in three cases personally observed by me produced a similar effect, and Ravdin and his collaborators<sup>51, 53</sup> have noted that the small bowel may assume the appearance of hypomotility and altered mucosal relief after a meal of olive oil. Possibly the malabsorption of fat is the sole responsible factor in the production of these changes in intestinal motility and contour.



FIG. 5. Characteristic roentgenologic appearance of the small intestine during an exacerbation of sprue. The alterations in mucosal relief and clumping and pooling of barium are conspicuous.

*Clinical Course of Nontropical Sprue.* Tables 2 and 3 give the essential data on the clinical course in the 32 cases of nontropical sprue observed at the clinic. It has been emphasized by many writers that both the tropical and nontropical varieties of sprue are extremely chronic diseases which do not present a static picture. With the passage of time, various complicating factors have developed in the cases reported here which greatly altered the general situation. Herein appear to lie some of the characteristic features of sprue of nontropical origin. In the course of partially or badly treated nontropical sprue a host of symptoms and signs which are distinctly secondary to the original ailment may develop. Many of these have been mentioned in some detail in the preceding paragraphs.

The course of events in two cases (Cases 4 and 8) serves to illustrate this point. The details of Case 4 are given in the appendix. This patient has been under observation at the clinic for eight years and came here originally because of a chronic digestive ailment attributed to duodenal ulcer. She returned at various times with the following symptoms in this chronological order: (1) marked nutritional edema, anemia and latent tetany; (2) severe active tetany requiring parathyroid hormone for its control; (3) bone pains (osteoporosis) and hypochromic anemia, and (4) marked pellagra with glossitis. The patient in Case 8, the details of which have been mentioned by Weir and Adams in their study of fat and protein metabolism in this disease, at first responded satisfactorily to liver extract, but a relapse subsequently developed which was characterized by marked hypoproteinemia and anasarca. Neither the diarrhea nor the general systemic symptoms of the disease were satisfactorily affected by liver extract thereafter, nor was it possible to elevate the plasma protein to a normal level although a complete control of the macrocytic anemia was effected up to the time of death.

If one reviews the data in tables 2 and 3 it will be noted that in 12 of the cases (1, 2, 3, 4, 5, 8, 15, 16, 19, 20, 21, and 30), the condition was of unusually long duration, or for various other reasons one or more such "complications" as those mentioned in table 4 had developed. Six of these cases were described in my earlier report and are of the type which might be designated by some authors as "idiopathic steatorrhea" but which I would now prefer to regard as examples of prolonged or poorly treated sprue. Eighteen cases (6, 7, 9, 11, 12, 13, 14, 18, 22, 23, 24, 25, 26, 27, 28, 29, 31, 32) were of the type identical with tropical sprue in that the patients' principal symptoms were glossitis, steatorrhea, chronic digestive disturbances, malnutrition and macrocytic anemia. In certain of these cases, notably Case 24, complications of one sort or another, most often incidental to lack of adequate treatment, were beginning to enter the picture. Details of Case 24, in which the patient was a resident of Minnesota, are given in the appendix. Two additional cases (10 and 17) are more difficult to classify, the steatorrhea being relatively less conspicuous than in the other cases; in both cases skin lesions and pigmentation complicated the picture.

Upon what do these differences in the clinical syndrome depend? A variability in the ability of the mucosa of the small intestine to absorb certain essential substances may be postulated but cannot be proved. Doubtless the distinctions between the various groups are largely artificial and would be largely eliminated if longer periods of observation in individual cases were possible. The condition, as emphasized before, is a dynamic one, and for this reason sharply defined classifications are necessarily based on somewhat insecure premises.

*Results of Treatment.* The specific effects of liver therapy in the treatment of tropical sprue are so well established as to find a place in definitive descriptions of the disease (Hanes<sup>18</sup>). It is therefore of particular interest to examine the results of such treatment of sprue contracted in northern latitudes in making comparisons between the two diseases. A detailed discussion of the treatment received by the various patients in the whole series of 32 cases of nontropical sprue must of necessity be omitted. Suffice it to say that over a 10-year period the types of treatment employed were not uniform, and only in the more recently studied cases has treatment been entirely adequate. In the first group of cases reported (Cases 1 to 10, tables 2 and 3), various types of sprue diets (high in protein and low in fat) were employed, and in most of these cases calcium salts and viosterol were also given. As Linder and Harris observed, these measures alone were often productive of surprisingly good results. The use of parathyroid hormone to control tetany was necessary in two cases, but it had no apparent effect on the general course of the disease. Various salts of iron, hydrochloric acid and vitamin concentrates were employed, with little effect in some of these earlier cases. Certain of these patients were given liver extract by intramuscular injection at various times (following the suggestion of Porter and Rucker) but in only three cases (4, 8 and 10) was it used in sufficient doses or for long enough periods to ensure an optimal effect.

In the second group of 22 cases (Cases 11 to 32), liver extract was employed by oral or parenteral administration in nearly all cases. As Bloomfield and Wyckoff noted originally, whole liver or liver extract by mouth was used with some success; this was true in Case 2 of this series. The patient in Case 5 has also remained well and able to do hard work over a six-year period on liver extract taken orally. On the other hand, a number of patients have received ventriculin at various times, but almost invariably without effect. The good effects which have followed the intramuscular injection of liver extract have been noted in cases of tropical sprue by Castle and Rhoads,<sup>10</sup> Miller and Barker and others. Equally satisfactory responses have been noted in many of our cases, although the results have not as a whole been so uniformly gratifying as in cases of tropical sprue. Nevertheless, in at least half of this series of cases of nontropical sprue liver extract produced reticulocyte responses and rises in erythrocyte counts which were comparable to those seen in adequately treated pernicious anemia, al-



though a considerably larger dose of liver was often necessary (figure 6). Nitrogen storage was favorably affected, as was shown by studies of metabolism in Case 8 and by sharp rises in serum protein in a number of others, notably Case 31, where an increase of 2 gm. per 100 c.c. was noted over a 60-day period. Utilization of fat has also been improved, as shown by the disappearance of fat from the stools and by the control of diarrhea. I have not repeated the experiments of Barker and Rhoads concerning failure of the post-alimentary rise in blood fats in sprue and the correction of this condition by liver extract, but one would expect that the results could be duplicated in this series of cases.

The appearance of the small intestine, as shown by roentgenologic examination, has been restored to a practically normal state within relatively short periods (one to two months) by the parenteral administration of liver

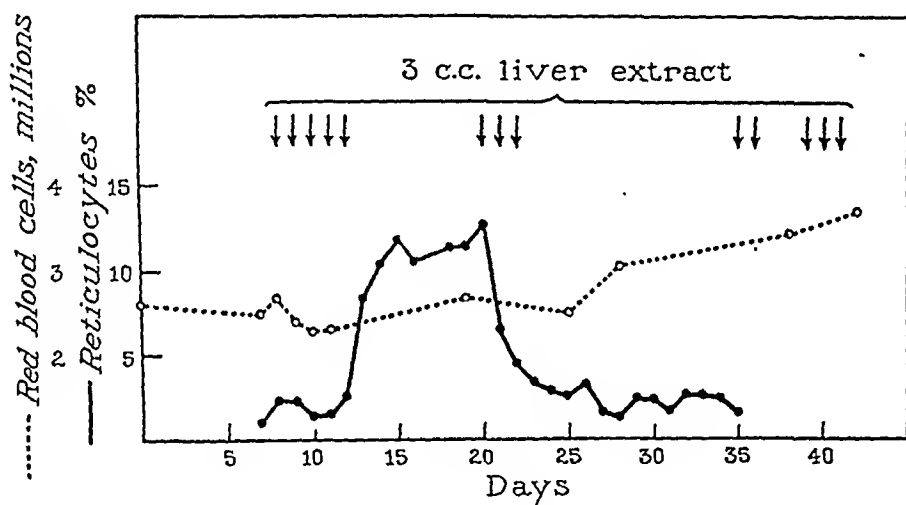


FIG. 6. Erythrocyte and reticulocyte responses to the parenteral injection of liver extract in sprue.

extract, a result which parallels exactly the observations made by Miller and Barker in tropical sprue (figure 7).

Insufficient data are available to warrant any conclusions as to the effect of liver extract on the typical "flat," glucose tolerance curve in this series of cases. All of the evidence in regard to calcium absorption and utilization is indirect; it does not appear from the clinic records, however, that liver extract of itself produced any material elevation in the level of serum calcium, although calcium is apparently stored better as fat absorption is improved. Nevertheless, calcium salts and viosterol are of obvious advantage in the treatment of patients with osteoporosis and tetany and they constitute an essential part of the treatment in such cases.

The general results of treatment in this series of 32 cases of nontropical

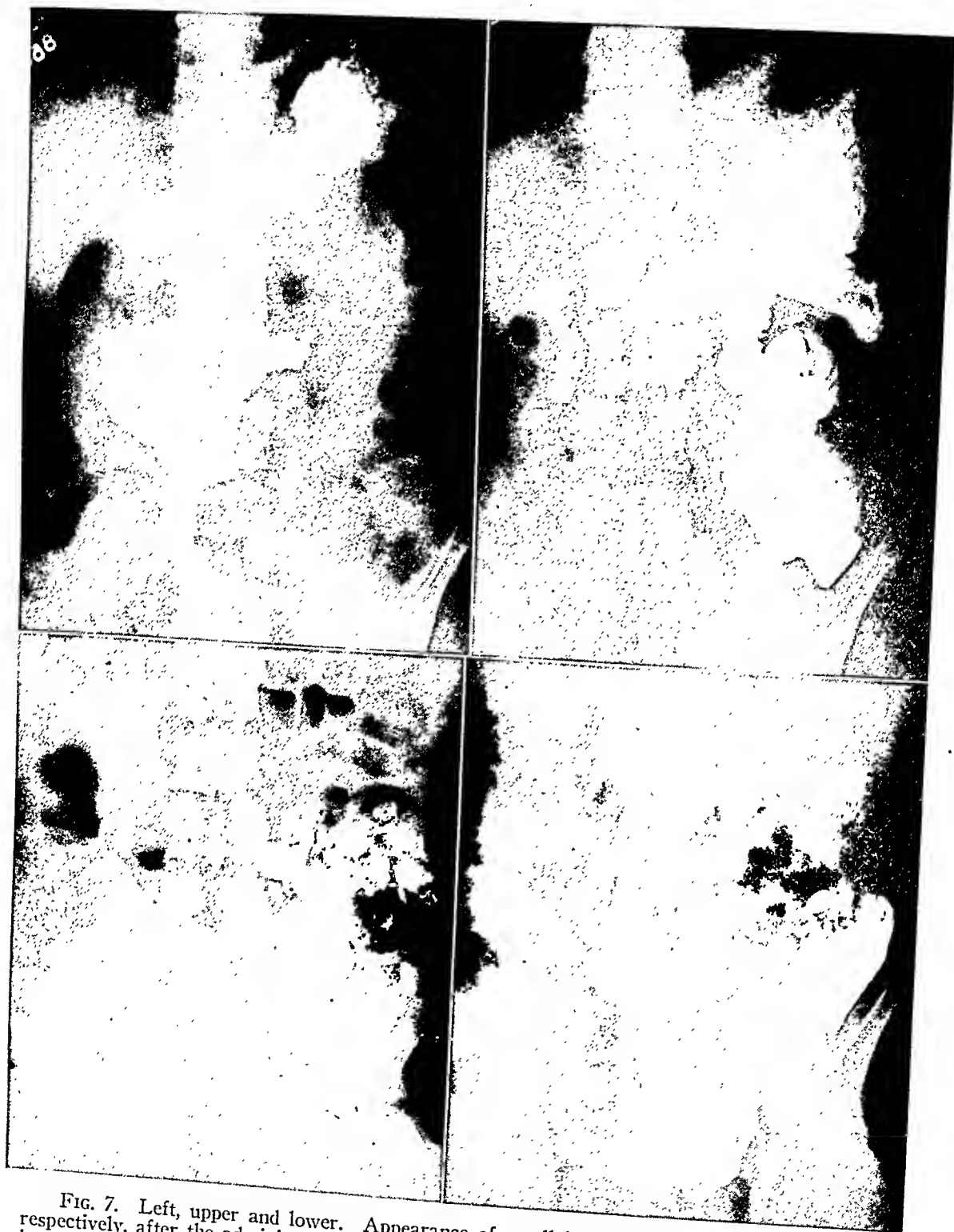


FIG. 7. Left, upper and lower. Appearance of small intestine 15 minutes and 6 hours, respectively, after the administration of barium; right, upper and lower, appearance of small intestine in same case after four months of treatment. The restoration of normal motility and reappearance of normal mucosal patterns are striking.

sprue are summarized in table 7. The preponderance of cases in which the treatment was successful is at once obvious. The failures require some comment. In Cases 1 to 10 there were four deaths, but only one of these patients (Case 8) really had prolonged and intensive liver therapy. In this case the anemia was corrected but the intestinal symptoms and hypoproteinemia continued. In the second group of 22 cases (Cases 11 to 32) there were six deaths; in three of these cases treatment with liver extract had been carried out, possibly in insufficient dosage. One of these patients (Case 30) died of a complicating disease (Landry's paralysis); a second patient (Case 29) had a complicating tuberculous, mesenteric lymphadenitis, and the third patient (Case 32) was a woman of 70 who had extensive general arteriosclerotic changes. Two patients died in relapse after discontinuing treatment with liver extract parenterally although such treatment

TABLE VII  
Response to Liver Extract

Patients		Response
Living		
15.....	Excellent	
1.....	Not used	
3.....	Ineffective	
1.....	Decreasing effect	
2*.....	No record (old series)	
22.....	Total	
Died		
1*.....	Not used	
6.....	Ineffective or partially so	
2.....	Relapse after discontinuing treatment or inadequate treatment	
1.....	Complicating disease	
10.....	Total	

\* Old series.

had previously proved effective. The other patient who died subsequently showed only slight response to liver extract parenterally; in this case extensive bony changes (osteoporosis) and marked malnutrition were present. In certain other cases liver extract parenterally was not completely effective because of insufficient dosage; however, even in these cases there was usually some temporary or partial response to its administration.

In general the failures, either partial or complete, occurred in the group of 12 cases previously mentioned in which the condition most closely approximated the picture of "idiopathic steatorrhea," using the term here in the sense of sprue complicated by marked disturbances in calcium metabolism, hypoproteinemia and multiple vitamin deficiencies. The successes, on the other hand, were most marked in cases in which the condition most nearly resembled tropical sprue. This observation recalls the fact that infantile celiac disease does not appear to be specifically affected by liver ex-

tract. In certain of these 12 cases (notably Case 4), however, persistent treatment with large doses of liver extract parenterally eventually brought about a satisfactory remission. There was reason to suspect that in certain other cases the intestinal tract had been damaged to a point where irreversible changes had occurred, with a resulting failure of intestinal absorption.

### ETIOLOGY

A discussion of the etiology of the sprue syndrome is not complete without some reference to the diseases which most closely simulate it. Fairley<sup>11</sup> must be credited with drawing attention to these conditions, of which the more important will be mentioned. Gastrocolic or duodenojejunal colic fistulas are of especial etiologic significance, and because of the short-circuiting of the small intestine produced by such lesions the picture of sprue may be simulated very closely. Fairley and Kilner's observations, as well as those of Mindline and Rosenheim, should be cited in this connection. We have record of one case at the clinic in which a gastrocolic fistula produced all of the usual symptoms of sprue, including macrocytic anemia, steatorrhea, nutritional edema and lowered concentration of blood calcium. Mesenteric lacteal obstruction will, as Langmead and later Fairley and Mackie have shown, simulate the sprue syndrome by cutting off the lymphatic channels through which fats are absorbed from the intestine. One of the patients referred to by them died with tetany and hypoglycemia. A patient has recently been observed at the clinic who had metastatic malignancy involving the retroperitoneal nodes, and the principal symptoms were highly suggestive of sprue.

The diseases most commonly confused with sprue, at least from the standpoint of diagnosis, are those in which destruction of the acinar tissue of the pancreas has been produced by a stone or tumor involving Wirsung's duct. In two cases in which the patients were observed at the clinic during the course of pancreatic lithiasis, sprue was closely simulated, the principal differentiating feature being the associated diabetes. One other patient with carcinoma of the pancreas presented himself at the clinic with steatorrhea, macrocytic anemia, and roentgenologic changes in the intestine which were typical of sprue. The development of obstructive jaundice shortly thereafter clarified the diagnosis of pancreatic neoplasm, which was confirmed at operation. In another case (seen in consultation, which case has recently been reported by Beard and Norris) the resemblance to sprue was very close. At necropsy a very small tumor was found blocking the pancreatic duct, with resulting pancreatic atrophy and marked fatty metamorphosis of the liver. Brems and Holst have cited somewhat similar cases which also illustrate the contributions to the clinical picture of sprue made by the steatorrhea alone. Some authors, in fact, have suggested that sprue is a manifestation of pancreatic insufficiency. The normal enzymatic activity of the duodenal contents in eight cases of this series should suffice to settle this contention.

These observations on the diseases which simulate sprue indicate certain common underlying factors and point to the relationship of failure of the absorptive function of the small intestine to the symptoms observed. The lymphatic block produced by retroperitoneal neoplasm achieves the effect of eliminating normal intestinal absorption by an indirect means. Why pancreatogenous steatorrhea will produce macrocytic anemia and sore tongue is not easily explained unless it is assumed that the presence of much undigested fat in the bowel may interfere with the absorption of certain essential portions of the vitamin B complex and the hematopoietic substance.

It has already been stated that there is much direct and indirect evidence to indicate that there is a specific failure of the absorptive function of the intestinal tract in sprue. This defect is apparently associated with, and may be caused by, some error in the absorption of the intermediary metabolism of the anti-pernicious-anemia principle or of some material with which it is closely allied. Liver extract containing this principle will, as has been demonstrated in all types of sprue, cure both the macrocytic anemia and the intestinal dysfunction.

Does the defective formation of the anti-pernicious-anemia principle, or its companion anti-sprue principle, constitute the first in a series of metabolic errors, or does small bowel dysfunction come first with failure to absorb the necessary hematopoietic principle developing secondarily? To review the large amount of evidence bearing on this question is beyond the scope of this paper. The correct and final answer is not known, but there are certain important observations bearing on the matter which must be mentioned. By feeding a modified Goldberger-Wheeler black tongue diet, a syndrome closely related to sprue may be produced in swine as well as loss of hematopoietic activity in the gastric secretions and livers of these animals (Miller and Rhoads<sup>45</sup>). These experiments, as Castle, Rhoads<sup>10</sup> and their associates<sup>46</sup> have noted, point to a cause sufficient to account for the secretory, and probably for the absorptive, defects in the patient with sprue. Miller and Rhoads have recently demonstrated that liver extract will produce not only functional improvement in the small bowel, but a return to its normal morphologic appearance, a fact which our experience at the clinic fully confirms. Jones and his co-workers have shown a similar improvement of the hypertrophic and atrophic gastritis associated with pernicious anemia under treatment with liver extract. One may conclude, with Miller and Rhoads, that one function of the anti-pernicious-anemia principle may be a conditioning of the functional activity of the small intestine and that this specific effect on the intestine is the one most characteristically produced in sprue.

On the foregoing basis, and following the observations of Castle, Rhoads and others,<sup>10</sup> a tentative explanation for the sequence of events in sprue, which is necessary for the discussion to follow, may be stated somewhat as follows: A lack of some unknown factor in diet, probably to be identified with some portion of the vitamin B complex, or a failure of the

intrinsic factor in gastric juice, may lead to failure of formation of certain products of digestion essential to the proper activities of the blood-forming organs and of the gastrointestinal tract. This deficiency, if not corrected, leads to progressive failure of the absorptive function of the small intestine; this involves a failure to absorb fat primarily, the absorption of carbohydrates and proteins being affected to a lesser degree. Deficiency in the absorption of calcium, which is closely associated with that of fat, likewise develops. Fat-soluble vitamins are poorly absorbed for the same reason; other vitamin deficiencies involving the water-soluble group are less conspicuous. With more or less complete failure in function of the small intestine continuing over a long period the complete picture of "idiopathic steatorrhea," as the term was used by Bennett, Hunter and Vaughan, with skeletal deformities, nutritional edema, tetany, cutaneous lesions and other deficiency symptoms, appears. This explanation would account for some of the distinctions which have been made between "idiopathic steatorrhea" and sprue and would agree with the observed effects of treatment in the two groups of cases mentioned in an earlier section of this paper.

#### DISTINCTIONS BETWEEN TROPICAL AND NONTROPICAL SPRUE

##### *Pathologic Changes*

Considerable attention has been directed toward the pathologic changes observed in fatal cases of both the tropical and nontropical varieties of sprue, and numerous reports on the matter, which are widely at variance with one another, have appeared. It is quite obvious that various types of chronic enterocolitis have been confused with sprue (Rosenthal) in certain recent reports, and that earlier investigators have been misled by postmortem changes in the intestinal mucosa. In tropical sprue, Mackie and Fairley<sup>35</sup> have described thinning and atrophy of the mucous membrane of the small intestine, with disappearance of the absorptive and secretory epithelium and atrophy of various organs and aplastic bone marrow. Low and Fairley cited an instance of fatal perforation of the cecum because of local thrombosis and ulceration of the thin and distended bowel. The most recent pathologic reports (Mackie and Fairley<sup>36</sup>) indicate that if the intestinal tract is removed and examined immediately after death, it will be found to be morphologically intact.

In nontropical sprue a variety of pathologic pictures, none of them particularly specific, have been described (Blumgart, Starr and Gardner). Lymphatic hyperplasia involving Peyer's patches and the mesenteric nodes has been mentioned, as well as submucosal edema of the digestive tract and atrophy of certain parenchymatous organs. Atrophy, dilatation, and passive congestion of the whole intestinal tract have also been described, with hemosiderosis of the liver and spleen. Lucksch and Sachs mentioned absence of the lymphatic apparatus in the small bowel, with fatty changes in the

liver. The files at the clinic contain records of three necropsies in cases of nontropical sprue. In one case (Case 30) in which the patient died of an intercurrent disease during a partial remission, the intestinal tract was entirely normal. In Case 29, reported by Mendez Ferreira and Barga,<sup>43</sup> a chronic, atrophic gastro-enteritis with mucosal atrophy and edema of the submucosa were noted. A third case (32) also showed marked atrophy of the mucosa of the digestive tract, with small ulcerations which were presumably part of a terminal process (figure 8).

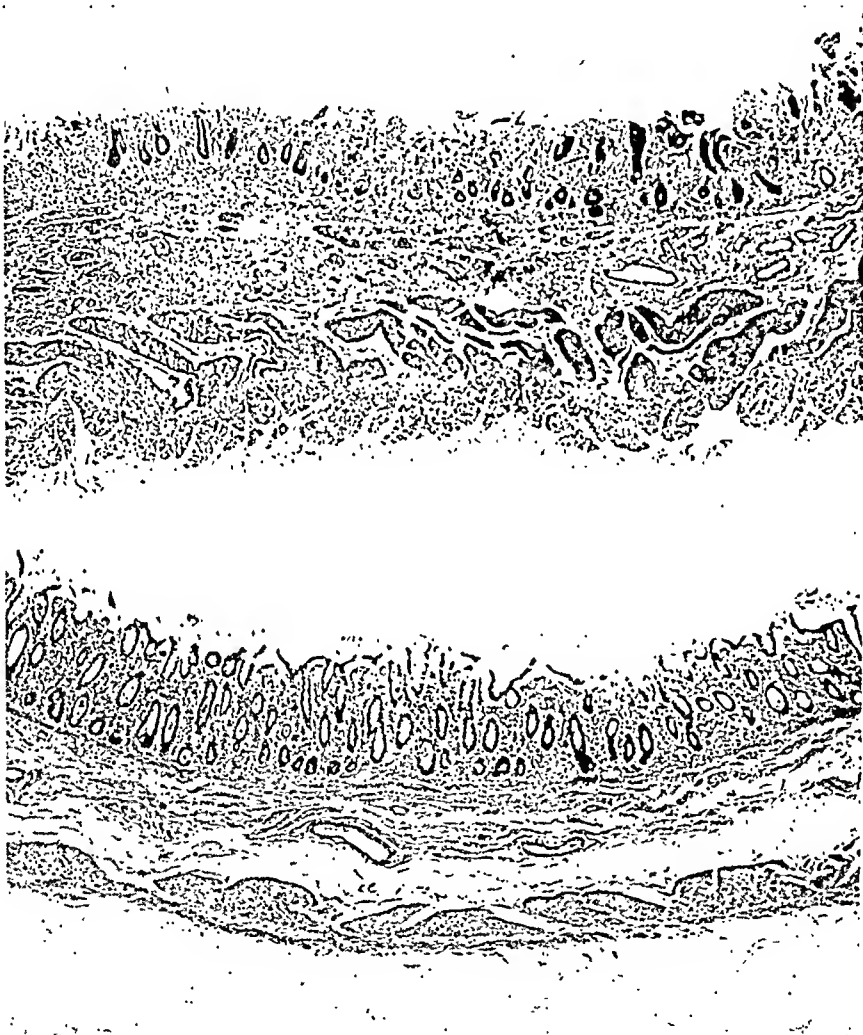


FIG. 8. Atrophy of the mucosa of the ileum in sprue (Case 32).

In short, there are no very significant differences between the pathologic picture in tropical and nontropical sprue except that, generally, the latter condition is most likely to show some definite changes in the intestinal tract. These changes, however, are neither specific nor characteristic. One must agree with Thaysen,<sup>62</sup> who has made an excellent summary of this matter, in his contention that the pathologic changes which have been observed in

both tropical and nontropical sprue are not significant, nor do they clearly differentiate one condition from the other.

What then are the significant differences between tropical and nontropical sprue? For reasons previously given one is forced to concede that the two types of sprue have a common basis in that a deficiency state is responsible for both. The age at which the disease makes its appearance doubtless has a definite bearing on the clinical picture, since the earlier intestinal dysfunction makes its appearance the greater the effects on growth and nutrition. The other differences in the clinical picture and response to treatment, which will be mentioned later, do not seem sufficiently great to warrant making any sharp differentiation between the two conditions. In the cases described by Bennett, Hunter and Vaughan, and in 12 of our series of 32 cases, there is much to suggest that the disease dated back to early life and in this sense may have had some relation to celiac disease. In many such cases irreversible and irreparable changes have doubtless taken place in the intestinal tract, in the skeleton, and in other viscera, and one would hardly expect specific treatment to be effective in every case.

Very active degrees of aphthous stomatitis and glossitis are apparently less common in nontropical sprue than in the tropical forms; the huge, fatty stools are also less conspicuous in sprue seen in temperate climates. Tetany and other disturbances in calcium metabolism are definitely more frequently observed in the latter group of cases. Fairley described tetany in 12 of a series of 80 cases of tropical sprue, whereas this phenomenon was noted in 9 of our 32 cases, certain of the patients having had latent tetany over long periods. Changes in the skeleton, such as osteoporosis and fracture, are said to be almost unknown in tropical sprue (Suarez); they are relatively common in the tropical form. It has been suggested that the high degree of ultraviolet radiation in the tropics may be a controlling factor in this difference. Hypoproteinemia and edema are also more frequently seen in nontropical sprue; the average figures for plasma proteins in our series of 32 cases were distinctly below those reported by Fairley for tropical sprue. Vitamin deficiencies in general are infrequently seen in tropical sprue but are common in the nontropical forms. Subacute, combined degeneration of the spinal cord has rarely been observed in tropical sprue (Giffin and others) but was noted in three cases in our series. From these facts one may assume that tropical sprue represents a milder form of intestinal dysfunction than sprue seen in temperate climates.

This may not be the only explanation, however. My personal conviction is that delay in diagnosis and failure to recognize and adequately treat the condition in its earlier stages are responsible for most of the observed variations. Both patients and physicians in the tropics where sprue is endemic are thoroughly familiar with the condition and quick to recognize it. In temperate climates, where it has long been thought that sprue was nonexistent, the diagnosis may be delayed for years, with resulting nutritional and metabolic disturbances which are almost beyond the reach of



treatment. As physicians at The Mayo Clinic have grown familiar with the sprue syndrome, the number of positive diagnoses has increased year by year and the condition is now being recognized and adequately treated before the stage of complete dysfunction has been reached. Most of the diagnoses have been made because of careful examination of stools and blood smears. As Hanes<sup>18</sup> has noted, a survey of old records of patients supposed to have had pernicious anemia will not infrequently reveal authentic cases of sprue; similarly, a search of cases with an indeterminate diarrhea and a poorly defined "deficiency state" will yield many examples of the sprue syndrome. If these facts are recognized, and if sprue is sought for as vigorously in northern climates as it is in the tropics, it seems certain that the artificial distinctions which have been set up between tropical and nontropical sprue will soon be regarded as unimportant.

#### CASE REPORTS

*Case 4. Nontropical sprue (observed over a period of eight years) with multiple complicating nutritional disturbances.* A farmer's wife, who lived in Wisconsin, registered at the clinic for the first time in February 1930, being at that time 43 years of age. At a very early age she had suffered from brief episodes of diarrhea and, at the age of 16 active tetany had developed. There had then been no further attacks until she reached the age of 23, when she had suffered annual, mild attacks of active tetany occurring most frequently in March or April.

At the time of her first examination the patient's principal complaint was of right upper abdominal pain which was projected to the back; she also complained of flatulence and distress after taking fatty foods. The physical findings were not remarkable; there was no anemia and an Ewald test meal showed a free hydrochloric acid of 48 and a total acidity of 62 units. A duodenal ulcer was demonstrated roentgenologically. Because of the possibility that this duodenal lesion might be penetrating, operation was advised. At operation a large duodenal ulcer was found which had produced much contraction and obstruction on the anterior wall of the duodenum. Posterior gastro-enterostomy was performed and the patient made a satisfactory recovery.

The patient had no further trouble until August 1930, when, following a respiratory infection, anorexia and diarrhea developed. Within a few weeks marked pitting edema of the legs was noted and active tetany again developed. On examination at the clinic at this time she was found to have a definite nutritional edema with serum protein of 4.1 gm. per 100 c.c. Chvostek's and Trousseau's signs were positive and the blood calcium was 6.8 mg. Blood studies showed a moderate hypochromic anemia, the value for hemoglobin being 12.4 gm. per 100 c.c. and the erythrocytes numbering 3,750,000 per cubic millimeter of blood. The hematocrit reading was 38 per cent. No free acid could be demonstrated in the gastric contents. The stools contained much excess fat and were voluminous in spite of a very small intake of food. The value for blood cholesterol was reduced—139 mg. per 100 c.c. Roentgenologic examination of the stomach and colon showed no evidence of gastrocolic fistula. The patient made a satisfactory recovery on a high protein diet with calcium lactate and viosterol and left the hospital in good condition with the diarrhea under control and no further evidence of tetany.

The patient returned for the third time in January 1931, with a recurrence of her former symptoms. At that time she had a marked, active glossitis and had lost a good deal of weight; a considerable degree of pigmentation was also noted over

the exposed surfaces of the body. No free acid was present in the gastric content even after stimulation by histamine. The stools still contained large quantities of fat. The value for hemoglobin was 6.5 gm. per 100 c.c. and erythrocytes numbered 3,700,000 per cubic millimeter. The blood smears showed a rather marked degree of hypochromasia, but the volume index was 1.04. While the patient was under observation very active tetany developed, with generalized convulsive seizures which persisted for several days and which were extremely difficult to control. Parathyroid hormone finally brought the level of blood calcium from 6.1 to 8.2 mg. per 100 c.c., but the serum protein remained low (5.5 gm. per 100 c.c.). The diarrhea was partially controlled by a high protein diet.

In June 1931, the patient made her fourth visit to the clinic. She was still emaciated and weak, her abdomen was distended, and the blood count had remained almost unchanged. The stools still showed an excess of fat and the hypoproteinemia and edema persisted. Blood transfusions, a high carbohydrate diet with restricted fat content, calcium lactate, viosterol and yeast were the principal therapeutic measures employed, under which the patient made some gradual improvement. At this time roentgenologic examination of the stomach for the first time showed hypomotility and distention of the jejunum. The patient continued to employ the dietetic and medical measures just mentioned with fairly good results for the next four years. She was seen at the clinic annually and her only complaints were of occasional bouts of diarrhea which ceased spontaneously.

In 1935, roentgenologic examination of the small bowel showed the hypomotility and distention typical of a deficiency state and roentgenograms of the long bones showed moderate osteoporosis. The hypochromic anemina and steatorrhea persisted. At this time a series of intramuscular injections of liver extract was begun; the patient had previously taken liver and liver extract intermittently by mouth with little benefit, but the parenteral administration of liver was continued intermittently for a year, with definitely beneficial effects.

In August 1936, the patient's son was killed in an automobile accident and the attendant shock and grief brought about a profound depression with almost complete anorexia. Diarrhea also developed and the patient neglected her medications, including the liver extract. In August 1937, she registered at the clinic in very poor condition, weighing only 87 pounds (39.5 kg.). There was marked edema of the lower extremities, atrophy of the tongue, neurologic evidence of polyneuritis and a marked pellagrous eruption over the lower extremities, neck and hands. Laboratory examinations were carried out following hospitalization. Urinalysis gave negative results. The hypochromic anemia persisted, the value for hemoglobin being 6 gm. per 100 c.c. and erythrocytes numbering 3,200,000 and leukocytes 4,400 per cubic millimeter. The blood calcium and phosphorus readings were, respectively, 7 and 4 mg. per 100 c.c. Undried stools contained about 18 per cent of solid fat by weight, of which about two-thirds was in the form of fatty acids. The serum protein was 4.6 mg. A glucose tolerance test taken after a brief period of treatment gave an essentially normal curve. Roentgenograms of the thorax and long bones were negative; those of the small intestine showed hypomotility but nothing else of significance. Roentgenologic examination of the colon again was made to exclude gastrocolic fistula, with negative results. Treatment with a high protein diet, large doses of brewers' yeast and liver extract parenterally resulted in slow but satisfactory improvement. At the time of her dismissal, five weeks later, the patient was taking a 3,000 calorie diet with little difficulty, but it was still necessary for her to restrict the fat content somewhat in order to avoid diarrhea. The serum protein had risen to 6 gm. per 100 c.c. and the blood calcium to 8.6 mg. The pellagrous eruptions and the nutritional edema had entirely disappeared. Moderate hypochromic anemia still persisted; the value for hemoglobin was 9.0 gm. and erythrocytes numbered 4,000,000.

The patient has progressed very well during the past year on a continuation of this same form of treatment and is in reasonably good condition at the present. She receives two injections of liver extract, each equivalent to 100 gm. of fresh liver, weekly. Her weight and strength are well maintained and no symptoms of sprue have been noted.

*Case 24. The syndrome of "tropical" sprue in a native of Minnesota.* A farmer residing in southern Minnesota, aged 41 years, registered at the clinic in March 1934. For the previous three years he had suffered from diarrhea for about six weeks out of each year, the attacks usually occurring during the autumn months. Flatulent indigestion and anorexia had been noted more or less continuously for about the same period. With the most recent attack of diarrhea he had suffered from paresthesias and cramps in his extremities, their description being very suggestive of tetany. He had lost about 30 pounds (13.6 kg.) and there had been a corresponding loss in strength. He said that he had not noted a sore tongue up to the time of his final examination.

On physical examination the patient was weak, undernourished and dehydrated. His tongue had a smooth, atrophic appearance but was otherwise normal. There was some pigmentation of the exposed surfaces of the body and clubbing of the fingers and toes was noted. Chvostek's and Trousseau's signs were negative. The abdomen was moderately distended with gas; no organs or masses could be felt. Neurologic examination showed no evidence of changes in the central nervous system. Laboratory examinations gave essentially negative results except for showing rather marked anemia. The value for hemoglobin was 10.8 gm. per 100 c.c. and erythrocytes numbered 2,860,000 and leukocytes 8,400 per cubic millimeter. The serum calcium was 8.9 mg. The morphologic appearance of the blood smears was very suggestive of pernicious anemia; an Ewald test meal showed free hydrochloric acid of 40 and total acidity of 54 units. The stools were not conspicuously fatty at the time of this first examination; however, a tentative diagnosis of sprue was made and treatment with whole liver by mouth was begun.

The patient returned to the clinic two months later. In the interval he recalled that there had been one earlier attack of glossitis which he had not remembered when first questioned about the matter. At the time of his second examination he was somewhat improved, although he still suffered occasionally from diarrhea and his appetite was still poor. His blood, however, was approximately normal, the value for hemoglobin being 16 gm. per 100 c.c. and erythrocytes numbering 5,240,000 and leukocytes 9,100 per cubic millimeter. Stained smears showed no significant abnormalities.

In February 1937, the patient again returned to the clinic. He had been quite well during the preceding year and had regained the weight which had been lost prior to his first examination. About a month prior to this registration, however, profuse diarrhea had developed and he had again lost about 30 pounds. He complained greatly of abdominal flatulence, cramps and marked anorexia. Physical examination gave essentially the same results as in 1934 except for increased distention of the abdomen. The stools were found to contain large amounts of fat and were offensive, yellow, foamy and voluminous. The blood counts were not remarkable; the value for hemoglobin was 14 gm. and erythrocytes numbered 4,000,000 and leukocytes 4,900. Morphologic study of the stained blood smears, however, showed typical macrocytosis. The serum calcium was 8.1 mg., phosphorus 2.1 mg., protein 5.5 gm. and cholesterol 150 mg. per 100 c.c. Roentgenograms of the small bowel showed the dilatation, hypomotility and irregularities of the mucosal pattern that are commonly seen in sprue. Definite osteoporosis of the spine and pelvic bones was also noted. Free hydrochloric acid was still present in the stomach; the test showed values of 10 units after an Ewald meal.

Because of the cachexia and severe diarrhea the patient was at once hospitalized for treatment. Liver extract in amounts containing the active principle from 100 gm. of fresh liver was injected daily for one week. Striking clinical improvement was noted at once. The diarrhea was checked, the patient's appetite returned, and there was a rapid gain in weight and strength. At reëxamination six months later the blood was entirely normal, both in respect to the cell counts and morphologic appearance of stained smears; the blood calcium and phosphorus had returned to normal levels and the serum proteins had increased to 6.3 gm. per 100 c.c. Roentgenologic examination of the intestinal tract showed definite improvement in the appearance of the bowel; however, there were still some abnormalities in the ileum and lower portion of jejunum. The osteoporosis was less marked than before.

Apparently the use of liver by mouth had induced a remission which lasted in this case for almost two years. The patient had also taken extralin and hydrochloric acid at various times, but the relapse which brought him to the clinic in 1937 had developed in spite of all these measures. The rapid and complete response of all of the symptoms and signs of sprue to treatment with liver extract parenterally was very striking.

#### SUMMARY AND CONCLUSIONS\*

A series of 32 cases of the sprue syndrome encountered in residents of temperate climates is reviewed and compared with examples of tropical

\* Since this article was submitted for publication a number of reports on the nature and treatment of nontropical sprue have appeared in the literature. Their importance warrants brief reference here. Brull and his collaborators [BRULL, LUCIEN, LAMBRECHTS, A., and BARAC, G.: Sprue nontropicale. Étude approfondie de quatre cas observés en Belgique, *Rev. Belge des Sci. Med.*, 1938, x, 457-532], in reporting an extensive metabolic study of four cases of the disease, have been impressed by the favorable effect on steatorrhea which followed the administration of vitamin B<sub>2</sub> (riboflavin) in two cases; they agreed that this observation needs further confirmation, but they pointed out that this phenomenon must be regarded as evidence favoring the idea that the fundamental feature of steatorrhea may depend on B<sub>2</sub> avitaminosis.

Bassett and his coworkers [BASSETT, S. H., KEUTMANN, E. H., VAN ZILE HYDE, H., VAN ALSTINE, H. E., and RUSS, E.: Metabolism in idiopathic steatorrhea. I. The influence of dietary and other factors on lipid and mineral balance, *Jr. Clin. Invest.*, 1939, xviii, 101-121], [BASSETT, S. H., KEUTMANN, E. H., VAN ZILE HYDE, H. and VAN ALSTINE, H. E.: Metabolism in idiopathic steatorrhea. II. Effect of liver extract and vitamin D on calcium, phosphorus, nitrogen and lipid balances, *Jr. Clin. Invest.*, 1939, xviii, 121-135], have likewise reported the results of their metabolic studies on four patients with "idiopathic steatorrhea"; in these cases striking calcium deficiencies and osteoporosis were present. Prolonged parenteral administration of liver extract to these patients failed to cause improvement in the absorption of fatty acids, calcium, phosphorus or nitrogen. These findings are in general accord with experience at the clinic in the treatment of patients presenting marked mineral and vitamin deficiencies, who were, as a rule, refractory to liver therapy.

Hotz and Rohr [Horz, H. W., and ROHR, K.: Die einheimische Sprue (Auf Grund von 22 eigenen Fällen), *Ergebn. d. inn. Med. u. Kinderh.*, 1938, liv, 174-268], in a comprehensive review of 22 personally observed cases of "einheimische Sprue" in Switzerland, gave an enthusiastic report on the general effects of liver therapy but did not check the effect on excretion of fat by metabolic studies. The gains in weight reported by them, however, compare with those noted in the clinic series; such rapid increases can hardly be interpreted as having occurred on any basis other than an improved capacity for intestinal absorption of foodstuffs generally.

Fanconi [FANCONI, G.: Zöliakie, *Deutsch. med. Wchnschr.*, 1938, lxiv, 1565-1568] and also Engel [ENGEL, RUDOLF: Sprue und Vitamine-K-Mangel, *Med. Welt*, No. 4, 1939], both have called attention to the probable defect of intestinal absorption in respect to the fat-soluble antihemorrhagic vitamin K and the relation of this defect to the hemorrhagic features which may characterize the disease.

sprue and with certain cases which have been classified as examples of "chronic idiopathic steatorrhea."

Twenty of the 32 patients presented symptoms and signs which were virtually identical with those seen in tropical sprue; these patients responded in a specific manner to liver extract. The remaining 12 patients presented various metabolic and nutritional disturbances, including tetany, osteoporosis, hypoproteinemia and various vitamin deficiencies. The condition in these cases was identical in all respects to that described in the English and Scandinavian literature as "idiopathic steatorrhea." The response to liver extract in these cases was often unsatisfactory, but in certain cases in which the patients were adequately treated, good results were obtained.

No fundamental difference between these two groups of cases was demonstrable, although it was apparent that intestinal dysfunction was more marked, or at least affected the absorption of more substances, in the smaller group of patients.

Distinctions among tropical sprue, nontropical sprue and idiopathic steatorrhea are largely artificial, the more intractable nature of the condition in the group of cases described under the last-mentioned caption being largely a matter of late diagnosis and inadequate treatment.

The sprue syndrome is not uncommon in temperate climates, and its earlier recognition and treatment would largely eliminate the late "complicated" cases.

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## GOLD THERAPY IN ARTHRITIS; OBSERVATIONS ON 100 CASES TREATED WITH GOLD SODIUM THIOSULPHATE AND AUROCEIN \*

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OUR interest in gold salts as a means of treating rheumatoid and osteo-arthritis was stimulated by the work of Dr. Jacques Forestier, who in 1934 published <sup>1a</sup> the results of his observations on 500 cases of rheumatoid arthritis, treated over a period of five years. He stated that it had previously been demonstrated by Mollgaard that injections of gold salts would arrest the progress of tuberculosis. It was rational, therefore, that the same remedy might be of service in other chronic diseases of infective origin. Forestier <sup>1b</sup> claimed that 70 to 80 per cent of the arthritic patients treated by him responded well to gold salt therapy.

In 1936, approximately nine years after he first introduced gold therapy in the treatment of arthritis in Europe, Forestier reviewed his experience with this type of treatment and reported <sup>1c</sup> that in chronic progressive rheumatoid polyarthritis the advance of the disease can be arrested by gold therapy in 85 per cent of the cases.

In 1937 Hartfall and Garland <sup>2</sup> reviewed 900 cases of chronic arthritis treated over a period of five years with gold salts. This was the largest series of cases reported up to that time. They obtained clinical improvement in approximately 80 per cent of the cases of rheumatoid arthritis and in more than 50 per cent of the cases of osteo-arthritis. The beneficial clinical results in the latter group were not comparable in degree, however, to those obtained in the rheumatoid group. Hartfall and Garland's <sup>2</sup> clinical observations have been confirmed by other European workers. Gerald Slot,<sup>3</sup> Pemberton,<sup>4</sup> Baker,<sup>5</sup> Crosby,<sup>6</sup> Buckley,<sup>7</sup> Sostberg, Schade, Steuber and Warburg <sup>8</sup> have all reported approximately the same results.

In the American literature only scant reference to gold therapy has appeared to date. Sashin and Spanbock <sup>9</sup> reported on 22 selected cases of active rheumatoid arthritis which they treated with gold salts intravenously with good results. Brief reports by Oren <sup>10</sup> and by Phillips <sup>11</sup> have appeared. Oren <sup>10</sup> reported on a series of 100 cases of various forms of arthritis. Of the 66 cases of atrophic arthritis in the series, 60 responded very well to the gold salt therapy. Twelve cases of gonorrheal arthritis all did exceedingly well. Of the 22 cases of hypertrophic arthritis, 13 cases improved under treatment. Phillips <sup>11</sup> treated 20 cases, nine of whom had atrophic or rheumatoid arthritis, eight hypertrophic or osteo-arthritis, two peripheral neuritis, and one subdeltoid bursitis. He used the technic advocated by Forestier.

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Only six of the 20 cases showed any subjective improvement and he consequently discontinued this form of treatment. Toxic reactions in his cases were numerous. Tegnier <sup>12</sup> writes, "European workers feel that up to date, gold salt therapy has not had a fair trial in the United States."

The American Committee on Rheumatism <sup>13</sup> is becoming more and more impressed by the number of favorable European reports on gold salt therapy (chrysotherapy) in arthritis. The American Committee is still uncertain, however, of the value of gold salts in arthritis and of the proper indications for their use. Hench <sup>14</sup> for example, writes, "Apparently definite benefit results from such therapy in an impressive number of cases, but until more controls are set up, we will not know the exact value of the method and how fully justified one is to run the risk of frequent and rather serious toxic reactions." Later, in the same review, he states, "Among the pitfalls in a study of therapy, is that of a dangerous but helpful drug; its full effect must be studied carefully, for what seems to be a dangerous drug today (e.g., gold) may be improved by further knowledge."

It is pertinent to observe at this point that there has been no uniformity among different investigators in the preparation of gold employed, the route of administration, the size of dose and number of doses per series, the number of series required, and the extent of adjuvant therapy during courses of treatment with gold.

Forestier himself <sup>1</sup> used several preparations, including myochrysine (sodium aurothiomalate), allochrysine (sodium aurothiopropyl sulfonate) and myoral (calcium aurothioglycolate). Hartfall and Garland <sup>2</sup> used myochrysine, crisalbine (sodium aurothiosulfate), and solgonal B (aurothio-glucose). Oren <sup>10</sup> employed Aurocein which he describes as a solution of sulfhydryl gold naphthyl trisulpho-carbonium derivative. Phillips <sup>11</sup> used myochrysine. The reasons for using the different preparations of gold are obscure, and appear to have been dictated by availability of the particular preparation, or by the desire to find one which is therapeutically effective and at the same time not toxic.

The mode of administration has also varied. The intramuscular route is preferred by some over the intravenous route because of ease of administration and gradual absorption of the drug. In general, the intravenous preparations, such as sanochrysin, contain approximately 40 per cent of metallic gold, whereas the intramuscular preparations, such as myochrysine, contain approximately 50 per cent of metallic gold. The mode of injection seems to have had little effect on either the therapeutic results or on the toxic reactions which sometimes have occurred.

Differences of opinion exist as to what should constitute the size of the initial dose, the number of doses and total dosage per series, and the number of series required. In regard to the initial dose, the general tendency has been downward. In their early work the European investigators gave from 200 to 500 milligrams, but because of the numerous toxic reactions which developed, the initial dose was more or less universally reduced to 50 milli-

grams. In the last three years the tendency has been to go even lower, and to start with 5 or 10 milligrams.

In regard to the total dose per series, opinion ranges from one gram (Hartfall and Garland,<sup>2</sup>) to 2.5 grams (Bach<sup>15</sup>). It would be futile to compare one set of figures with another, as there is such variability from worker to worker in the preparation of gold used, the mode of administration, and frequency of injections and the type of patients studied.

Rest periods between series of injections vary from four to eight weeks (Forestier and Bach), to two to three months (Hartfall and Garland and Buckley) to six months (Baker).

Relapses of arthritic symptoms are not uncommon after the first course. They seldom occur after the second course of treatment in patients who respond favorably. The most usual time for the appearance of relapses is about six weeks after the completion of the first course. Forestier<sup>1</sup> consequently advises beginning the second course of treatment one month after completion of the first. Hartfall and Garland,<sup>2</sup> on the other hand, believe that the interval between completion of the first course and commencement of the second should be at least two to three months, in order to avoid the possibility of injecting additional gold salts into a patient who may be on the verge of a delayed toxic reaction.

Recurrence of arthritic symptoms should never discourage the physician from giving a second series of injections. The experience of many workers<sup>2</sup> has been that, while one series may fail to benefit or completely relieve the patient with rheumatoid arthritis, the second series is often followed by complete and permanent relief.

All European workers<sup>2</sup> agree that, despite the greatest care in the administration of gold, toxic reactions are encountered in 40 to 50 per cent of the cases. The most common toxic manifestations are cutaneous irritations (particularly pruritus) and gastrointestinal upsets. These mild reactions are relatively unimportant and clear up within a few days or weeks. About 15 per cent, however, manifest more severe reactions, such as generalized exfoliative dermatitis, severe gastrointestinal disturbances, jaundice and even aplastic anemia. These severe toxic reactions may last for a year or longer and may even prove fatal.

Jaundice developed in 9.4 per cent of Hartfall and Garland's<sup>2</sup> cases. They pointed out, however, that this high percentage should not be regarded as the ordinary incidence of toxic jaundice following gold therapy because two patients in their clinic who were not on gold therapy developed jaundice coincidentally, and that there was a mild epidemic of infectious jaundice in that region from which most of their cases were drawn. It is interesting to note that most of their cases treated with gold salts which developed jaundice became worse during that period. This is in direct contrast with the experience of Wyatt and Thompson,<sup>16</sup> who purposely produced jaundice in 10 cases of rheumatoid arthritis by administering relatively large doses of bile salts and bilirubin intravenously. They stated that this combination

had an ameliorating effect on the symptoms of atrophic arthritis. Hench<sup>14</sup> has also noted that patients with rheumatoid arthritis treated at the Mayo Clinic were completely free of arthritic symptoms during the period that they suffered from jaundice, and that their arthritic symptoms usually reappeared following the disappearance of the jaundice.

The mechanism responsible for the toxic reactions in gold therapy is unknown. In animals approximately 80 per cent of the gold is excreted in the first 24 hours and the remaining 20 per cent is deposited in the mesenchymal tissues.<sup>2</sup> Toxic reactions may be due to hypersensitivity of patients to even minimal doses, or to accumulation of gold in the tissues beyond a critical level.

The mode of the therapeutic action of gold in arthritis is likewise unknown. In this respect its empirical use may be likened to the employment of arsenic and mercury in syphilis. Forestier and Certonciny<sup>1</sup> believe gold has no direct effect on the etiologic factor in arthritis, but that it checks the progressive inflammatory changes in the joints. At least part of the beneficial effects may be due to what, for want of a better term, is called "shock therapy." The writers have repeatedly seen in their own practice instances in which a slight overdose of gold produced a reaction similar to a foreign protein reaction, accompanied by chills, fever and leukocytosis. It is probable, however, that an additional factor is present, since patients who have previously shown no improvement on vaccine therapy respond to gold. In this connection, it is interesting to note that Yanagisawa and Kawai<sup>17</sup> point out that the only gold compounds which produce beneficial results are those which contain sulphur. In the treatment of experimental tuberculosis in guinea pigs they found that one of their gold salt compounds was just as effective when the gold radicle was removed and the sulphur radicle left in.

To determine this point, we have analyzed 50 milligrams of gold sodium thiosulphate and found that it contains 12.5 milligrams of sulphur. It seems to the authors, from their experience in giving sulphur therapy, that it is questionable if this small dose of sulphur, given once a week, could have any beneficial effect on the arthritic patient.

To date there is not available a method for determining hypersensitivity to gold. The intravenous use of vitamin C or calcium gluconate has not proved of help in preventing or neutralizing toxic reactions. When reactions do occur, there is no known method for shortening the attack except by ceasing treatment with the drug until all evidence of toxicity has disappeared.

After a study of the available literature on gold salt therapy in arthritis, the present writers began to use this form of therapy at the Arthritis Clinic of the Hospital for the Ruptured and Crippled. The cases chosen were those that had proved to be refractory to all other accepted methods of treatment. We believe that this is the best way to set up a control series to test the relative efficacy of any new form of treatment.

In our series, the following precautions were taken routinely in an effort to avoid needless toxic reactions:

1. Hypersensitive patients or patients with any history of skin, liver, kidney or intestinal irritability were eliminated from this study.

2. Before beginning treatment, each patient had a complete blood count, urinalysis and determination of his sedimentation rate. During treatment, frequent examinations of the patients' urine were carried out, and if any specimen showed the presence of albumin or urobilinogen, where previously the urine had been negative, treatment was usually discontinued until the urine became normal again. In some cases, we found that the presence of albumin in the urine was not a contraindication to further treatment if given cautiously. Blood counts and sedimentation rate studies were also carried out at frequent intervals during the course of treatment.

3. Each patient thoroughly understood the possibilities of failure as well as the possibilities of toxic reactions before treatment was instituted.

4. The gold salts solution was prepared freshly by dissolving the powdered salt in 5 c.c. of triple distilled sterile water immediately before injection. The solution was injected slowly. All injections were administered by one physician. The clinical results of treatment, however, were observed and estimated by the three authors after personal recall interviews with each patient.

5. The intravenous method of administration was used because we thought it was easier to observe the immediate results. In those cases which presented technical difficulties, Aurocein was used intramuscularly. This preparation contains a 5 per cent solution of sulfhydryl gold naphthyl trisulpho-carbonium derivative and comes in 2 c.c. ampules. A series consisted of two injections a week for six weeks, making a total of 12 injections per series, with an interval of one month or six weeks between series. If any toxic reactions appeared we discontinued the injections immediately and did not renew the medication until all symptoms of toxicity had subsided. In subsequent treatments, we lengthened the interval by giving one ampule a week.

6. We preferred to use gold sodium thiosulphate because it was the salt originally used by Mollgaard in 1924. It has been used extensively with success in lupus erythematosus and in arthritis over a period of 14 years, and its relative toxicity has been fairly well established. Further advantages of the Abbott gold sodium thiosulphate used in this series are that it is an American product, is easily obtainable and it has been approved by the Council on Pharmacy and Chemistry of the American Medical Association. Moreover, Forestier<sup>1</sup> pointed out that gold sodium thiosulphate was apparently less toxic, although slightly less efficient than the other commonly used gold salts.

7. Dosage: The initial dose of gold sodium thiosulphate was 5 milligrams. If no toxic reactions developed, the dose was increased by 5 milli-

grams and then by larger amounts according to the schedule found below:

1. 5 mg.	5. 50 mg.	9. 100 mg.	13. 100 mg.
2. 10 mg.	6. 75 mg.	10. 100 mg.	14. 100 mg.
3. 15 mg.	7. 100 mg.	11. 100 mg.	Total 990 mg.
4. 35 mg.	8. 100 mg.	12. 100 mg.	to each series.

As can be seen, the highest dose given was usually 100 milligrams. In only one case did we go up to 125 milligrams. The total dosage in a series exceeded 1000 milligrams in only one case. A series usually consisted of 12 to 15 injections and rest periods were from six to eight weeks. Two series of injections were given to those patients who could tolerate the treatment. However, there is no contraindication to giving additional series, up to five series, if the preceding treatment does not entirely cure the patient, provided the interval between series is lengthened by at least one month between series.

To the extent that chronic arthritis cases can be classified clinically, the 100 cases consisted of a group of 50 with rheumatoid arthritis, of 20 with osteo-arthritis and of 30 with a mixed form of arthritis. The criteria for evaluating the results in this study after gold therapy were as follows:

Excellent results: Complete cessation of all subjective symptoms, disappearance of swelling, return to normal range of movement, ability to sleep and to return to gainful occupation.

Good results: Diminution of pain and swelling and increased motion of involved joints.

Fair results: Diminution of pain or swelling or lessening of restriction of joint motion.

Poor results: No change or improvement.

The results obtained in the 100 cases of chronic arthritis are shown in table 1.

TABLE I

	Rheumatoid cases	Osteo cases	Mixed cases
Number of Cases.....	50	20	30
RESULTS:			
Excellent results.....	1	none	1
Good results.....	5	4	0
Fair results.....	18	5	7
Poor results.....	26	11	22

In the rheumatoid group therefore, 24 out of 50, or 48 per cent of the patients showed some degree of clinical improvement. In the osteo-arthritic group, nine out of 20, or 45 per cent showed improvement, while in the mixed group, eight out of 30 patients, or 26 per cent improved. Of the entire group therefore, 41 per cent showed some degree of clinical improvement following gold salt therapy. This is a definite and substantial

percentage of improvement in cases that did not respond satisfactorily to other accepted forms of arthritic therapy.

Forestier<sup>1</sup> and Hartfall and Garland<sup>2</sup> emphasized that the efficacy of gold therapy in chronic arthritis is in inverse ratio to the duration of the disease. We classified our cases into two groups: those who had the disease for less than two years, and those who had been ill for two years or longer (tables 2 and 3.) In the group that gave a history of less than two years' duration, there were 14 rheumatoid, seven mixed and five osteo-arthritic cases. In the group of over two years' duration, there were 36 rheumatoid, 23 mixed and 15 osteo-arthritic cases. In the group that gave a history of

TABLE II

Clinical Results Following Gold Therapy in Arthritis Cases of Less Than Two Years' Duration

	Rheumatoid cases	Mixed cases	Osteo cases
Number of Cases.....	14	7	5
RESULTS:			
Excellent results.....	0	1	0
Good results.....	1	0	2
Fair results.....	8	1	1
No change.....	5	5	2

TABLE III

Clinical Results Following Gold Therapy in Arthritis Cases of More Than Two Years' Duration

	Rheumatoid cases	Mixed cases	Osteo cases
Number of Cases.....	36	23	15
RESULTS:			
Excellent results.....	1	0	0
Good results.....	2	0	2
Fair results.....	13	6	4
No change.....	20	17	9

less than two years' duration, 54 per cent of the cases improved in some degree. In the group of patients who had the disease for over two years, only 38 per cent showed improvement. Our results therefore, are in agreement with those of previous workers.

One sees statements in the literature<sup>1, 2, 12</sup> that gold therapy is more effective in patients of the early and middle age groups than in those of the latter decades of life. We have classified the patients in this study under separate age groups: 20-40 years; 40-50 years; 50-60 years; and 60 years and over. The results in these age groups are summarized in the following table:

TABLE IV  
Results of Gold Therapy in Arthritis According to Age Groups

	Rheumatoid cases	Mixed cases	Osteo cases
Age 20-40	19	6	4
RESULTS:			
Excellent results.....	0	0	0
Good results.....	2	0	1
Fair results.....	7	1	0
No change.....	10	5	3
Age 40-50.....	16	11	3
RESULTS:			
Excellent results.....	0	1	0
Good results.....	1	0	1
Fair results.....	7	4	0
No change.....	8	6	2
Age 50-60.....	10	9	9
RESULTS:			
Excellent results.....	0	0	0
Good results.....	2	0	2
Fair results.....	4	2	2
No change.....	4	7	6
Age 60 or over .....	5	4	4
RESULTS:			
Excellent results.....	1	0	0
Good results.....	0	0	0
Fair results.....	2	1	3
No change.....	2	3	1

From these statistics, it is evident that improvement in the age group 20 to 40 occurred in over 37 per cent of the cases, while in the age group of 40 and over, improvement occurred in over 45 per cent of the cases. Our results, therefore, are at variance with previously published statistics and indicate that advancing age is no contraindication as to the use of gold therapy.

The sedimentation rate of red blood cells did not always prove to be, in our experience, a reliable index for judging clinical progress. For example, in the improved group of cases where one would ordinarily expect a lowered sedimentation rate, 47 per cent of the cases showed an elevated sedimentation rate at the end of the period of treatment. On the other hand, in those cases in which no clinical improvement occurred, we found that in 80 per cent of the cases the sedimentation rates showed a lowered level at the end of treatment. This series has only been carried on over a two year period. Over a longer period of observation these figures will perhaps change and our experience may conform with the experience of European workers.

Toxic reactions were observed in 17 patients. In 11, dermatological lesions formed the outstanding symptoms. These were in the nature of localized or generalized rashes, which persisted generally from three days to a week. In one case, the skin rash lasted two and one-half months. This



patient emphasized to us the latent danger of administering gold therapy since he had had only two intravenous injections of gold sodium thiosulphate (sanochrysin) which were given a week apart. He received 10 milligrams at the first injection and 20 milligrams at the second injection. The rash appeared immediately after the second dose. There were also four cases with gastrointestinal disturbances characterized chiefly by nausea and anorexia. These symptoms, however, cleared up promptly. Edema of the hands and feet occurred in two cases. In a third case, the development of edema proved to be alarming because it involved the glottis. This patient was delirious for three days, had increasing dyspnea and had to be relieved finally by tracheotomy. This patient also had had only two intravenous doses, a total of 30 milligrams of gold sodium thiosulphate. After recovery from the toxic reaction, this patient who had rheumatoid arthritis has now been completely free of all arthritic symptoms for a period of one year. There have been no fatalities.

### SUMMARY

In this series, we have attempted to determine the therapeutic effects of gold salts in the treatment of arthritis, as well as their limits of safety. Our observations warrant the following statements:

1. Gold may be given as gold sodium thiosulphate (sanochrysin) intravenously, or sulphydryl gold naphthyl trisulpho-carbonium (Aurocein) intramuscularly, without serious permanent injury in the great majority of patients, if reasonable precautions are observed. These precautions include careful selection of patients, small initial doses and gradual increase in dosage, and constant vigilance for evidences of toxicity.

2. In the rheumatoid group, 24 out of 50 patients (48 per cent) showed definite clinical improvement according to our criteria. In the osteo-arthritic group, nine of 20 patients (45 per cent) improved, while in the mixed group, eight of 22 patients (26 per cent) showed improvement. Of the entire group therefore, 41 per cent showed some degree of clinical improvement following gold salt therapy. The criteria for improvement are discussed. Our percentages of successful results in cases refractory to usual methods of treatment were not as good as those reported by European workers, but their series included early and untreated cases of arthritis, many of which might have been cured by other methods of treatment.

3. We feel that our clinical results would have been better had larger doses been employed, or had we used one of the stronger salts, but toxic reactions would have been more numerous and more alarming.

4. In the present status of our knowledge, gold salt therapy appears to be too dangerous for general use. It should be undertaken only when the case is refractory to the usual forms of treatment. The risk involved should be explained to the patient before treatment is instituted.

5. There is no standard procedure for the administration of gold salts.

Increasing experience may lead to a standardized therapeutic procedure. The mode of action of gold salts and their optimal dosages require further investigation.

6. In our series, the percentage of toxic reactions was only 17 per cent. The majority of these manifestations were mild in degree. Three cases in whom more serious reactions occurred, eventually showed improvement in their arthritic symptoms.

7. At the present time, we have 200 cases under treatment. This group will be enlarged and we hope to submit a further report at the end of five years.

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# RIGHTWARD DEVIATION OF THE AXIS OF THE T-WAVE AS AN INDEX OF MYOCARDIAL DISEASE \*

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THE clinical significance of the height of the T-wave in Leads I and/or III of the electrocardiogram has been approached from different angles by different authors. Eideiken and Wolferth<sup>1</sup> studied low  $T_1$ , low  $T_1$  and  $T_2$ , and low  $T_2$  with inverted  $T_3$ . They point out that a  $T_1$  less than 2 mm. in height is usually associated with myocardial disease unless the position of the heart is vertical. In the latter case the non-significant low  $T_1$  is generally associated with a low  $R_1$ . These authors do not consider the electrical axis of the T-wave except as far as the changes in amplitude in the several leads may reflect axis changes. In the course of a study of left axis deviation, Proger and Minnich<sup>2</sup> emphasize three signs which accentuate the abnormality of the picture. These are low T-waves in Lead I, high T-waves in Lead III, and deep S-waves in Lead II.

As a result of observations made by us during the past several years, we have become convinced that the electrical axis of the T-wave is of more significance than mere lowness or highness of a T-wave expressed in millimeters. For example, an upright  $T_1$  of 1 mm., even when  $R_1$  exceeds 6 mm. in height, is not necessarily significant when all the T-waves are low. It consequently appears desirable to attempt a more general formulation of the problem expressible in quantitative terms, but simple enough to be practicable for routine use. The latter requirement today rules out the method employed by Wilson, Macleod, Barker and Johnston<sup>3</sup> which depends upon the determination, by use of a planimeter, of the net positive or negative areas of the QRS complexes and of the T-waves.

The method of analysis herein described is an outgrowth of observations made several years ago (Ashman and Hull,<sup>4</sup> page 89). We found, from an analysis of the electrocardiograms of 100 normal adults, that while  $T_1$  was either higher or lower than  $T_3$  when the average electrical axis of the QRS complex lay to the right of about  $+30^\circ$ , the  $T_1$  was always higher than  $T_3$  when there was a left axis deviation, with an exception to be noted below. Since that time we have watched the  $T_1/T_3$  ratio and have become convinced that it is one of the most valuable electrocardiographic signs. This paper presents our conclusions regarding it.

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## METHOD

Several hundred electrocardiograms, the majority of which showed a  $T_1$  lower than  $T_3$ , were taken at random from our files. After elimination of incomplete and complete bundle-branch blocks, inverted T-waves in Lead I, most of the inverted T-waves in Lead III and all cases in which the diagnosis of heart disease was reported as doubtful, we had remaining 587 electrocardiograms. Inverted  $T_3$  did not come within the scope of this study. For each electrocardiogram, the average QRS axis and the ratio of the height of  $T_1$  divided by height of  $T_3$  were determined. Other abnormalities, if present, were noted. A record was also kept of the presence or absence, and the relative amplitudes of the S-waves in all leads, and of the R-wave in Leads I and II.

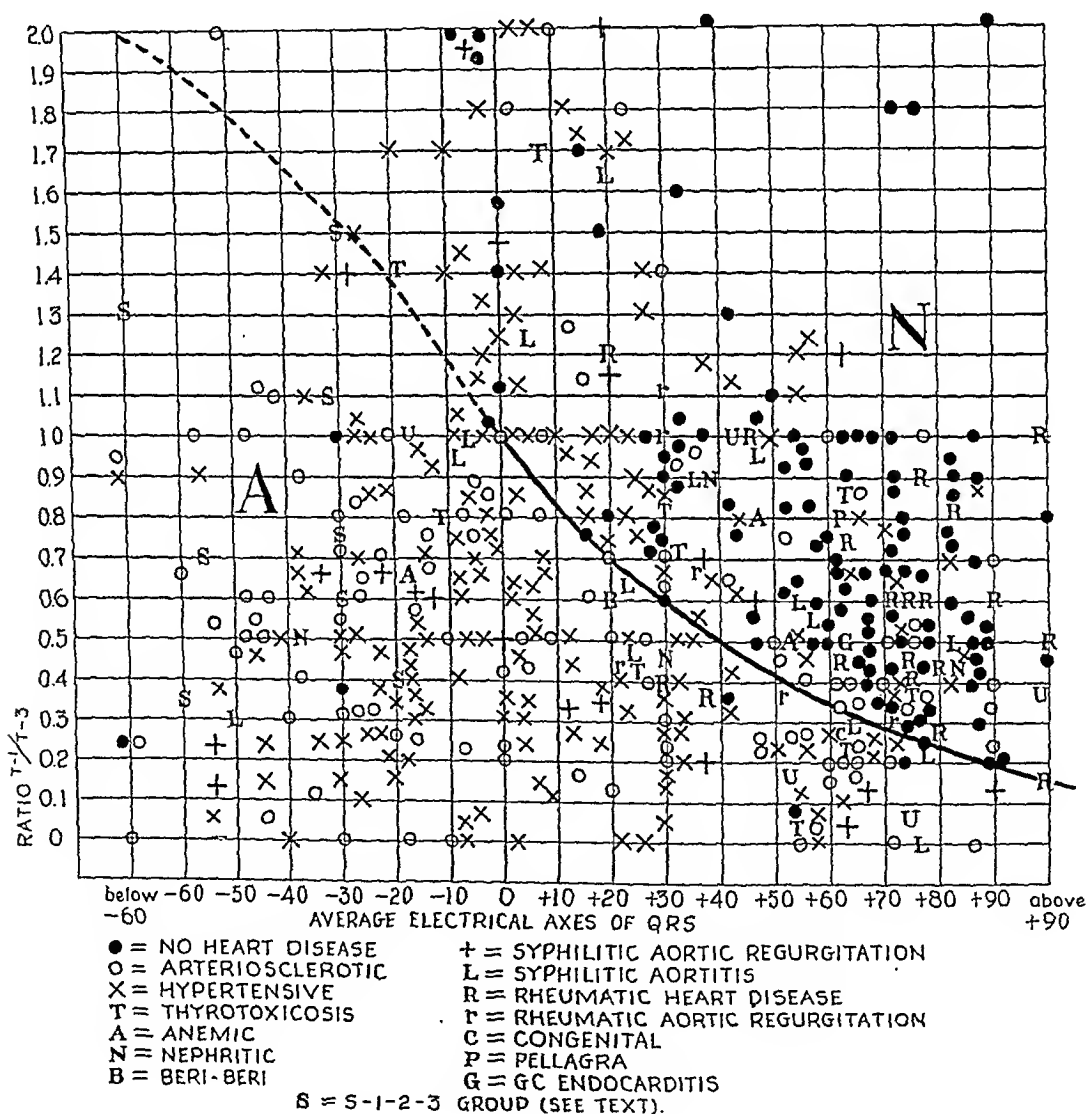


FIG. 1.

The  $T_1/T_3$  ratio might have been expressed as the electrical axis of the T-wave, and the latter may readily be derived from the former. We felt the ratio to be more convenient.

## RESULTS

The average electrical axes of the QRS complexes and the  $T_1/T_3$  ratios were plotted as shown in figure 1. The primary etiological factor is indicated by the sign used for each point, as explained on the figure. The points marked S constitute a special group which will be discussed below.

It will at once be seen that the great majority of the small black discs, corresponding to patients with no demonstrable heart disease, are located to the right of the oblique curved line. The placing of the line means, therefore, that according to our data, the ratio  $T_1/T_3$  is normally smaller the more the average electrical axis of QRS inclines to the right, and vice versa. In damaged hearts, the normal ratio may be disturbed, as indicated by the points to the left of the line. We may say at once that we regard the area, N, above, and to the right of, the line as the normal, and the area A, below, and to the left of, the line as the abnormal area.

In table 1, only those points which fall between the ratios 0 to 2.00 are included in the subsequent analysis. Above 2.00 the ratio is normal for any QRS axis, except possibly extreme left axis deviations, while axes below 0, due either to  $T_1$  or  $T_3$  inversion, do not concern us. If we count the cases in each area, we find the following:

TABLE I

Etiology	Abnormal Area		Normal Area		Heart Station Population— 500 cases Per Cent
	Number	Per Cent	Number	Per Cent	
No heart disease.....	6	2.5	101	42.4	22.6
Arteriosclerotic heart disease.....	77	32.0	33	13.8	17.0
Hypertensive-arteriosclerotic.....	115	48.0	59	24.8	35.0
Syphilitic aortic regurgitation.....	16	6.7	6	2.5	6.2
Syphilitic aortitis without regurgitation.....	8	3.3	7	2.9	4.6
Thyrotoxic.....	6	2.5	5	2.1	3.2
Rheumatic heart disease without aortic regurgitation.....	3	1.2	17	7.1	4.6
Rheumatic heart disease with aortic regurgitation.....	2	0.8	4	1.7	1.8
Congenital.....	1	0.4	0	0	1.0
Nephritic without hypertension....	2	0.8	2	0.8	0.6
Anemic.....	1	0.4	0	0	1.8
Pellagra and beri-beri.....	1	0.4	1	0.4	0.4
GC endocarditis.....	0	0	1	0.4	0
Traumatic.....	0	0	0	0	0.4
Unknown.....	2	0.8	2	0.8	0.6
Totals.....	240	99.8	239	99.7	100

It will be seen from the table that 42.4 per cent of the 239 patients in the normal area were considered not to have heart disease, leaving 57.6 per cent who were diseased. In contrast, only 2.5 per cent (excluding the S group) in the abnormal area were considered to be without heart disease, leaving 97.5 per cent diseased.

The S group consists of eight patients, none of whom had demonstrable heart disease, and whose electrocardiograms are of a special and not very unusual type. There is either no trace, or the slightest trace only, of a Q-wave in any lead.  $R_2$  is higher than  $R_1$ . A definite S-wave is present in all three leads, although  $S_1$  is sometimes small. Both  $S_2$  and  $S_3$  are large. No upward deflection follows S in any lead. Among our 587 cases, 29, with QRS axes of  $+20$  or below, fell into this category. Only four of these 29 patients presented  $T_1/T_3$  ratios lying within the normal area, but no doubt more would have done so had not our selection of electrocardiograms been mainly of the low  $T_1$  type. Of these 29 cases, eight had no demonstrable heart disease; 19 had arteriosclerotic hypertensive heart disease; one, a male aged 44, was diagnosed beri-beri; while in another case the diagnosis of arteriosclerotic heart disease was regarded as doubtful. The percentage in this group without heart disease, 27.6, may be compared with the percentage of normals in the Heart Station population, or 22.6. Eleven of the 21 cases with definite or probable heart disease presented definite electrocardiographic abnormalities, while this was true of only one of the eight without demonstrable heart disease, and here the abnormalities (a P-R at the upper limit of the normal and a wide, but otherwise normal, P-wave) were borderline. None of the eight patients even approached the hypersthenic habitus. A transverse heart is not, therefore, usually responsible for this picture. On the contrary, it seems more characteristic of the vertical or normally placed heart. We have observed many other electrocardiograms of this type in patients without heart disease. We shall call such electrocardiograms the  $S_{123}$  type.

Special attention should be directed to the six patients without definite heart disease and not of the special  $S_{123}$  type, whose T-wave ratios fall in the abnormal area. On reexamining the first case, at  $75^\circ$  and ratio 0.20, we find that because of irregularity of the base line, the amplitude of  $T_1$  was doubtful. Reconsideration shows that it is unquestionably higher than as measured. This case actually, therefore, comes in the normal area and can be disposed of. We let it stand because of the obvious dangers to objectivity involved in reconsideration of difficult cases. The second case, at  $55^\circ$  and 0.07, is a colored male, 43 years of age. Although classified as normal, syphilitic aortitis was regarded as possible. The third case, at  $44^\circ$  and 0.35, was a colored male, aged 58. The peripheral arteries were sclerosed, but his heart was not enlarged and there were no cardiac symptoms. The fourth case, at  $-30^\circ$  and 0.38, was a white male, aged 50. His Wassermann was 4 plus and a diagnosis of tabes dorsalis had been made.

He complained of sharp pains "in his heart" on exertion or excitement. The fifth, at  $-30^\circ$  and 0.75, was a colored male, aged 28. He complained of rather severe, smothering, substernal pains on working, but nothing was found on physical examination. The Wassermann was negative. The sixth case, at  $65^\circ$  and 0.25 was a white male, aged 23. There was a marked deformity of the sternum which was sunken, forming a deep sulcus (funnel chest). He had experienced a right-side hemiplegia four months previously. A review of these six cases, therefore, indicates that in most of these instances the diagnosis of no heart disease was questionable.

Returning to the table, it will be seen that the various etiologic factors are not equally effective in producing abnormal  $T_1/T_3$  ratios. Arteriosclerotic heart disease, without hypertension, constitutes 32.0 per cent of the abnormal and only 13.8 per cent of the normal ratios. The added presence of hypertension does not increase the tendency of the T-wave axis to deviate to the right. It should be noted that no attempt was made to separate the "essential" hypertensions or hyperpiesias from the hypertensive cases in which a nephritic factor was present.

If we may draw any conclusion from the small number of cases, syphilitic heart disease with damage of the aortic valve is just as potent, or even more potent, a factor than arteriosclerotic heart disease; while syphilitic aortitis, without valvular involvement may sometimes effect a rightward deviation of the axis. Thyrotoxicosis also appears to be effective, but this may depend upon factors other than the increased basal metabolic rate.

In contrast to the hypertensive-arteriosclerotic etiology is rheumatic heart disease when the aortic valve is not involved. The numbers indicate that this factor has little or no tendency to deviate the T-axis to the right. As a check against these figures, we have examined the electrocardiograms of the 100 children with rheumatic heart disease reported elsewhere by Drawe, Hafkesbring and Ashman.<sup>5</sup> Of these, 8 per cent showed abnormal ratios. Rather unexpectedly, the group with aortic valve disease showed no greater incidence of the abnormality than the others. These observations suggest that while rheumatic heart disease may sometimes cause an abnormal rightward deviation of the T-wave axis, such deviation is relatively infrequent. On the other hand, there is also no greater tendency for the T-axis to shift to the left.

It might be supposed that if there is enough myocardial damage to produce an abnormal  $T_1/T_3$  wave ratio, the electrocardiogram would nearly always be otherwise abnormal. To afford information on this point, we give the data for the 68 electrocardiograms in the abnormal T-wave ratio area whose QRS axes are above  $+20^\circ$ . Of these, 11 cases, or 16 per cent, showed such extreme abnormalities of other kinds that the abnormal T-ratio was hardly needed as additional confirmation of the findings. There were 23 cases, or 35 per cent, in which the other abnormalities were moderate. In this group the evidence from the T-ratio was distinctly helpful. Finally,

33 cases, or nearly 49 per cent, showed no other abnormalities or such slight ones that their interpretation as abnormal depended entirely or almost entirely upon the abnormal T-wave ratio. In this latter group, of course, would fall many electrocardiograms whose QRS axes were below  $+21^\circ$ , but these are not here included because in them the left axis deviation itself might be regarded as abnormal.

It may be of some interest to observe, in figure 1, how the individual points just above, and to the right of, the oblique line and to the right of  $+30^\circ$ , are predominantly from patients with heart disease of the hypertensive-arteriosclerotic type. As the points lie deeper and deeper in the normal area, the proportion of such cases declines and that of no heart disease rises. This indicates that in many persons with heart disease the T-axis has begun to shift, but has not yet gone over into frankly abnormal territory. Perhaps a consideration of the anatomical axis of many of these hearts would indicate that their T-wave axes are, in fact, abnormal.

### DISCUSSION

The result of these comparisons suggests very strongly that rightward deviation of the T-axis is a result of disease of the left ventricle. Usually, but perhaps not always, the disease appears to be due to a relative or absolute inadequacy of the coronary circulation. Such inadequacy is obvious enough in arteriosclerotic-hypertensive heart disease. In aortic regurgitation the coronary flow is relatively inadequate; it fails satisfactorily to meet the increased oxygen demand resulting from the augmented ventricular diastolic volume. When syphilitic aortitis gives rise to symptoms, the orifices of the coronary arteries are likely to be involved by the pathological changes. Thyrotoxicosis, by increasing the oxygen demand, as well as the work, of the heart may often give rise to a relative coronary insufficiency. The left ventricle presumably suffers more than the right in these conditions, as is generally recognized, and as is indicated by the higher incidence of pathological changes in the left ventricle.

Myocardial depression or disease resulting from diphtheria does not cause a rightward deviation of the T-axis. On the contrary, the tendency is for it to shift to the left (Ashman and Hull<sup>4</sup>).

*Large S<sub>2</sub>.* Proger and Minnich<sup>2</sup> have emphasized the importance as a sign of myocardial disease of a large S-wave in Lead II in left axis deviation. We are very much inclined to doubt the value of the large S<sub>2</sub> as an independent sign, for, in general, the larger the S<sub>2</sub> the greater the left axis deviation. It is the latter finding, and not the S<sub>2</sub>, which is significant. Our data were analyzed from this standpoint and the results may be summarized as follows:



TABLE II

Electrical Axis	Large S <sub>2</sub>		Moderate S <sub>2</sub>		Small S <sub>2</sub>		Trace of or No S <sub>2</sub>	
	No H.D.	H.D.	No H.D.	H.D.	No H.D.	H.D.	No H.D.	H.D.
-40 to -59°.....	1	24	0	1	0	0	0	0
-20 to -39°.....	4	35	1	20	0	7	0	0
0 to -19°.....	2	19	3	32	3	28	3	11
+ 1 to +20°.....	1	5	4	21	0	29	2	34
Totals.....	8	83	8	74	3	64	5	45

It will be seen that there is no significant increase in the proportion of cases with no heart disease as the S<sub>2</sub> wave becomes smaller. However, as the electrical axis rises from about +20, the incidence of cases with no heart disease rises. This is indicated by the table below, which is a continuation of table 2, and which follows the same headings.

TABLE III

+21 to +40°.....	0	5	9	14	8	28	3	15
+41 to +60°.....	2	2	5	9	11	26	6	20
Totals.....	2	7	14	23	19	54	9	35

These figures serve to emphasize the importance of the average electrical axis of QRS as an index of myocardial disease. In making an evaluation, however, the position of the heart must be considered, and the special S<sub>1 2 3</sub> group already described must be eliminated.

*Low T<sub>1</sub>.* Another question which we have incidentally investigated is the absolute magnitude of T<sub>1</sub>. Except for vertically placed hearts, Eideiken and Wolferth<sup>1</sup> place the lower limit of the normal height of T<sub>1</sub> at 2 mm. Our experience is in rather sharp contrast with their findings. The 100 adult normals, reported by Ashman and Hull,<sup>4</sup> had an average amplitude of T<sub>1</sub> of 1.7 mm. On reexamining our records, we find that 51 of these subjects (or 51 per cent.) had T-waves in Lead I ranging from 1.8 mm. to 0.2 mm. The next lowest T-wave in this normal series was, however, 0.7 mm. Five of the 51 subjects were described as of hypersthenic habitus and their T<sub>1</sub> amplitudes were, respectively, 1.7, 1.4, 1.8, 1.3, and 1.5 mm., the corresponding average QRS axes being 62, 71, 0, 58 and 57°. Among the hundred individuals, not one had an abnormal ratio. The individual whose T<sub>1</sub> measured 0.2 mm. belonged, very clearly, in the S<sub>1 2 3</sub> group. It is not easy to explain the discrepancy between our findings and those of Eideiken and Wolferth. It may be that the T-wave tends to be lower in warm climates, a difference possibly associated with a lower basal metabolism (Hafkesbring and Borgstrom<sup>6</sup>). In this connection, it may be pointed out

that the average amplitude of  $T_1$  as found by Lewis and Gilder<sup>7</sup> was 1.93 mm. The average amplitudes found by us were consistently about 0.2 mm. lower than theirs in each lead. But this small difference is quite insufficient to explain the discrepancy. The inclusion of a large number of young adult males in Eideiken and Wolferth's series may have some bearing on the difficulty, for the T-wave of males, both in children and in adults, is higher than that of females (Lincoln and Nicolson,<sup>8</sup> Pardee<sup>9</sup>). In a recent unpublished comparison, for example, we find the average height of the highest T-wave of the three leads to be about 2.65 mm. in adult males, against about 2.10 mm. in adult females.

### SUMMARY

In heart disease, and probably particularly when the left ventricle is more involved than the right, a rightward deviation of the electrical axis of the T-wave is a common finding. The deviation is most frequent in arterio-sclerotic-hypertensive and in syphilitic heart disease; it is common in thyrotoxicosis; it is sometimes, but not often, seen in rheumatic heart disease.

The decision as to whether or not a given T-wave axis is abnormal depends upon the average electrical axis of the QRS complex.

A diagram is given which tentatively separates the normal from the abnormal T-wave axes at different QRS axes.

A special ( $S_{123}$ ) type of electrocardiogram is described which is easily recognizable and which constitutes an exception to the general rule.

The significance of deep  $S_2$  and of low  $T_1$ , as isolated findings, is discussed.

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# CASE REPORTS

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## HYPERTENSION AND CONSTRICTION OF THE RENAL ARTERIES IN MAN: REPORT OF A CASE\*

By EBNER BLATT and IRVINE H. PAGE, *Indianapolis, Indiana*

WE have recently studied a patient in whom the kidneys, adrenal glands, abdominal aorta, inferior vena cava, ureters, and renal vessels were enveloped in a firm mass of lymphosarcoma. This patient had arterial hypertension, and, since the renal vessels were markedly compressed by the tumor, it is suggested that this hypertension simulated that produced in dogs by constricting the renal arteries (Goldblatt, Lynch, Hanzal and Summerville<sup>1</sup>).

### CASE REPORT

The patient was first studied at the Cincinnati General Hospital in February 1937. He had had edema of the face, neck, and chest for one week. Roentgen-ray examination showed a right pleural effusion which had displaced the mediastinum to the left. Widening of the superior mediastinum and moderate infiltration of the right lung were observed several weeks later and were attributed to a lymphoblastoma. Partial superior vena cava obstruction was indicated by increased venous pressure in the arms.

He received roentgen-ray therapy from March until August 1937, when he was readmitted to the hospital with edema of the ankles. Venous pressure determinations now indicated partial obstruction of the inferior vena cava.

A week after admission he became drowsy and began to vomit. The blood urea nitrogen was 125 mg. per cent and the CO<sub>2</sub> combining power 26 volumes per cent. He was given large amounts of fluid intravenously and improved rapidly. All signs of uremia disappeared within three weeks. Repeated urine examinations showed no red blood cells and only a trace of protein. During his admission to the hospital arterial pressure varied from 150 mm. Hg systolic, 110 diastolic, to 135 systolic, 105 diastolic. The possibility that the uremia had been due to constriction of the renal arteries by a retroperitoneal tumor was suggested by the members of the staff of the Cincinnati General Hospital at this time.

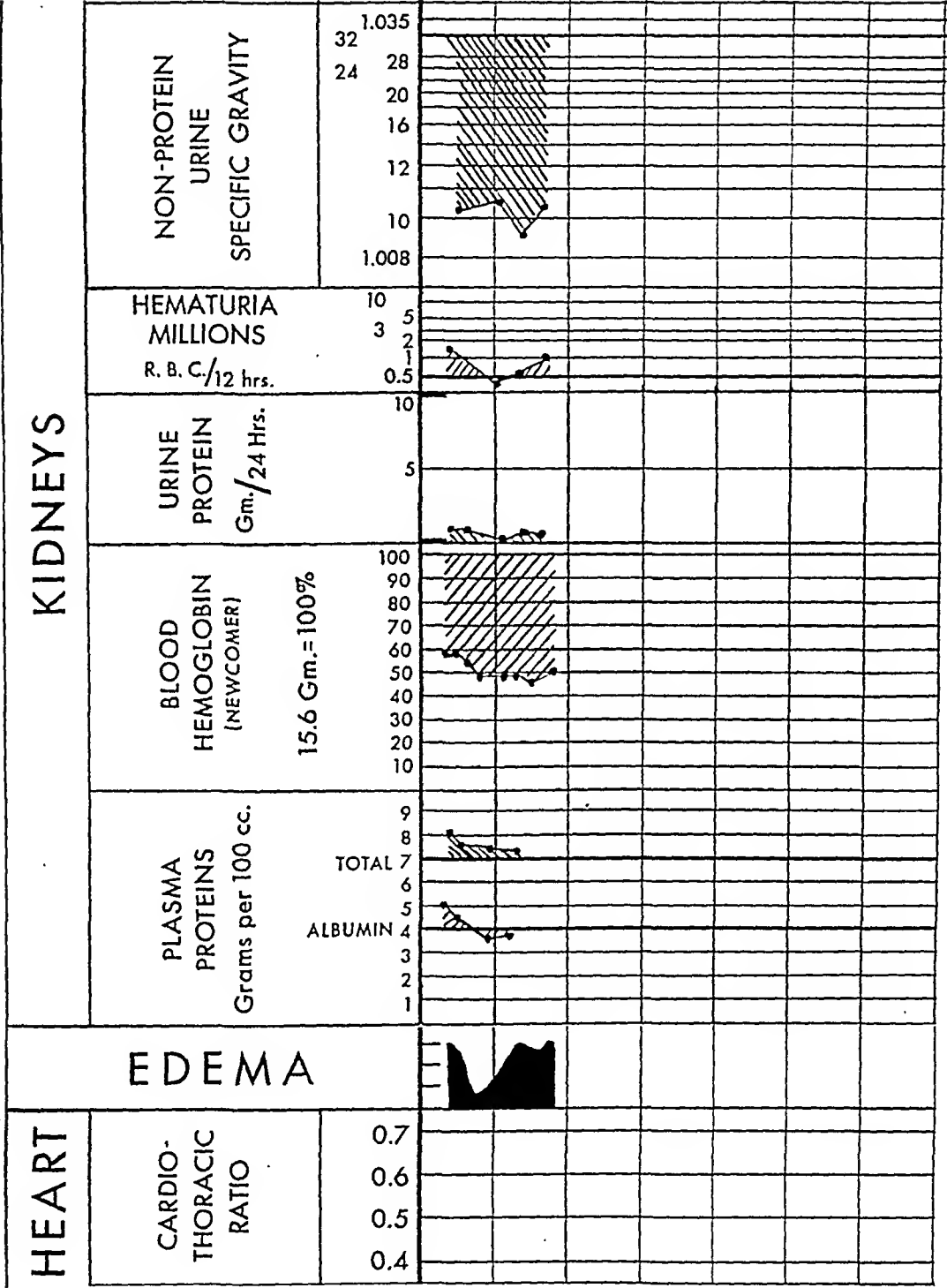
In October 1937, he began to have nocturia, and edema of the lower extremities recurred. He had had severe vomiting for several weeks before he was first seen at the Indianapolis City Hospital on November 9, 1937.

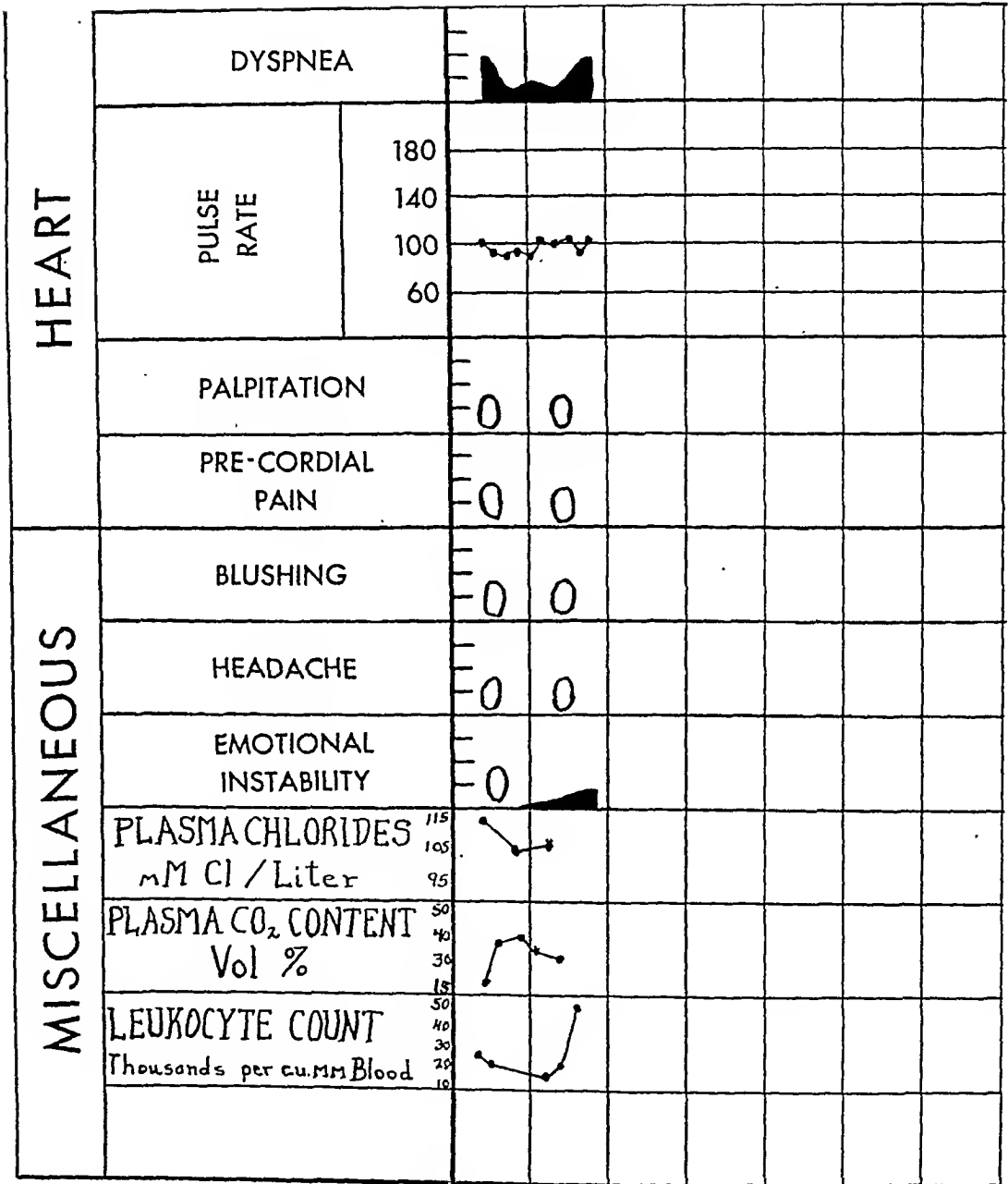
Physical examination now revealed marked pitting edema of the legs from the hips down. The scrotum was markedly edematous. There was slight edema of the eyelids and face. The heart was normal. There was fluid in the base of the right chest. The retinæ showed a few small fresh hemorrhages and slight constriction of the arterioles. The blood pressure was 204 mm. Hg systolic, 110 mm. diastolic. The blood non-protein nitrogen was 250 mg. per cent and urea clearance 2.9 per cent of normal. (The results of the laboratory examinations are summarized on the accompanying graph.) Roentgenograms of the chest showed no evidence of a tumor.

\* Received for publication March 26, 1938.

From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis, Indiana.

No.		Hosp. No. 464		F.Y., ♂		38 yrs.	
LYMPHOSARCOMA							
10 MONTHS				1	2		
BLOOD VESSELS	BLOOD PRESSURE	280					
		260					
		240					
		220					
		200					
	180						
160							
140							
120							
100							
80							
FUNDUS CHANGES	Cstr. art.						
	Sclr. art.	0	0				
	Exudate	0	0				
	Ret. hem.						
	Pap. Edem.	0	0				
KIDNEYS	UREA CLEARANCE % average normal	120					
		100					
		60					
		40					
		30					
		20					
		15					
		10					
		8					
		6					
		5					





For about a week after admission edema continued to increase, and the patient's condition rapidly became critical. Since he had what appeared to be a lead line on the upper gum and increased numbers of reticulocytes and stippled red cells in his blood, he was given calcium carbonate and potassium bicarbonate by mouth, and calcium levulinate intravenously.

The patient seemed to improve for a week. Edema decreased and he lost 25 pounds of weight. Blood pressure dropped to 152 mm. Hg systolic, 102 diastolic and urea clearance rose to 9.5 per cent of normal. The venous pressure in his arms which had been 200 mm. of water was now 88 mm.

Edema of the lower extremities reappeared and increased steadily until his death. Arterial pressure rose to its previous high levels and urea clearance decreased. He began to show marked emotional instability. Two days before death he developed pain in the right side of the chest, dyspnea, fever, and tachycardia. Death occurred about 11 months after the onset of the disease.

*Autopsy* (Dr. H. C. Thornton and Dr. J. McFadden). There was a large firm neoplastic mass over the posterior abdominal wall. It enveloped the aorta, inferior vena cava, kidney, renal vessels, adrenal glands and ureters, and extended down into the pelvis and around the bladder. The mass and the structures involved in it were removed in a single piece weighing 1245 grams.

The aortic orifices of the renal arteries appeared normal in size, but cross sections through the mass showed that the arteries were constricted throughout their course. There was some hydronephrosis in both kidneys. The ureters were constricted throughout all but the terminal portions of their course.

Sections of the neoplasm proved it to be a lymphosarcoma composed of lymphoid cells and a reticular network of fine and coarse strands of connective tissue. Irregular infiltration of the lymphoid cells was present in both kidneys and was most marked around the hila. The outer epithelial layer of Bowman's capsule in many glomeruli was hypertrophied. The capillary lumina were narrowed and were empty of blood. The tubules were somewhat atrophic and their epithelium flattened. The kidney pelves were normal. The arteries within the kidneys were normal but the walls of the veins were infiltrated with lymphocytes. The ureters were normal except for constriction.

The adrenals were completely imbedded in the neoplasm but on microscopic examination the cells appeared normal.

The right lung was partially collapsed by cloudy fluid. The pleural surfaces of both lungs were grayish white with exudate. There was no consolidation in either lung.

The pituitary gland, liver, heart, spleen, pancreas, bladder, prostate, stomach, intestines and brain were normal both on gross and microscopic examination.

The bone marrow was normal on inspection but microscopic study showed it to be very cellular with preponderance of lymphoblastic cells.

## DISCUSSION

Since the lymphosarcoma involved the kidneys, renal vessels, ureters, abdominal aorta, inferior vena cava and adrenal glands, and since the kidneys showed histologic evidence of early glomerulonephritis, the possible factors entering into the genesis of arterial hypertension in this patient are numerous.

The hemorrhages in the retinae, constriction of the retinal arterioles, proteinuria and hematuria, although all of minor degree, suggest the occurrence either of chronic glomerulonephritis or of essential hypertension. However, from pathological examination, the evidence of glomerulonephritis was slight.

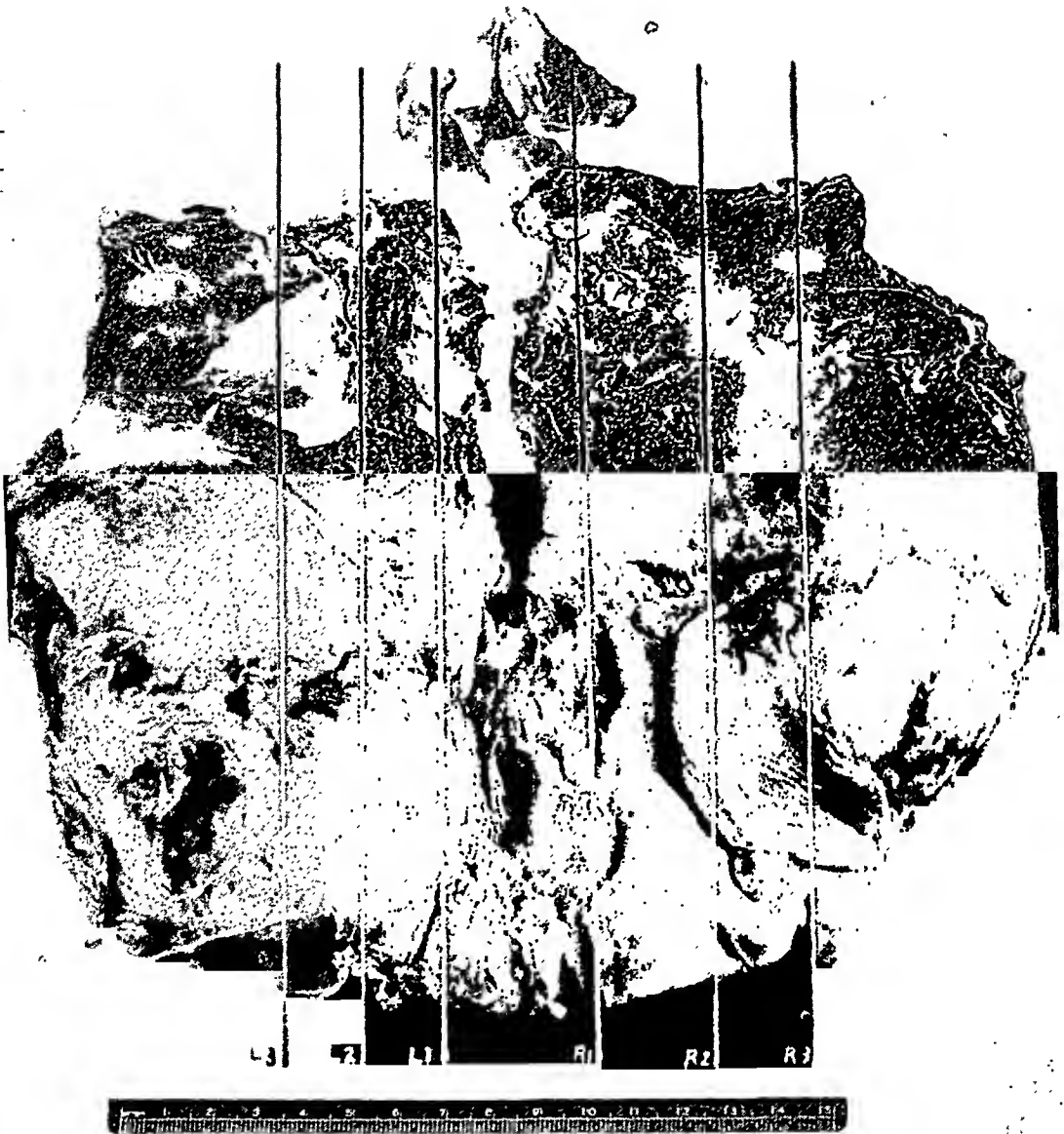


FIG. 1. Posterior view of lymphosarcoma and structures enveloped in it. The aorta is partially opened. The white lines indicate planes through the mass which are shown in figure 2.

It consisted of hypertrophy of the outer layer of Bowman's capsule, hyalinization in a few glomeruli, and atrophy of some of the tubules. The absence of cardiac hypertrophy and of widespread degenerative changes in the arteries, and the relatively short duration of the disease mitigate the probability of essential hypertension.

Among the methods designed to produce hypertension of renal origin are: reduction of the amount of functioning renal tissue; permanent or temporary occlusion of the renal arteries, veins, and ureters; passive hyperemia by constriction of the renal vein; permanent or temporary obstruction of the ureters; and compression of the kidneys by an oncometer. With most of these methods



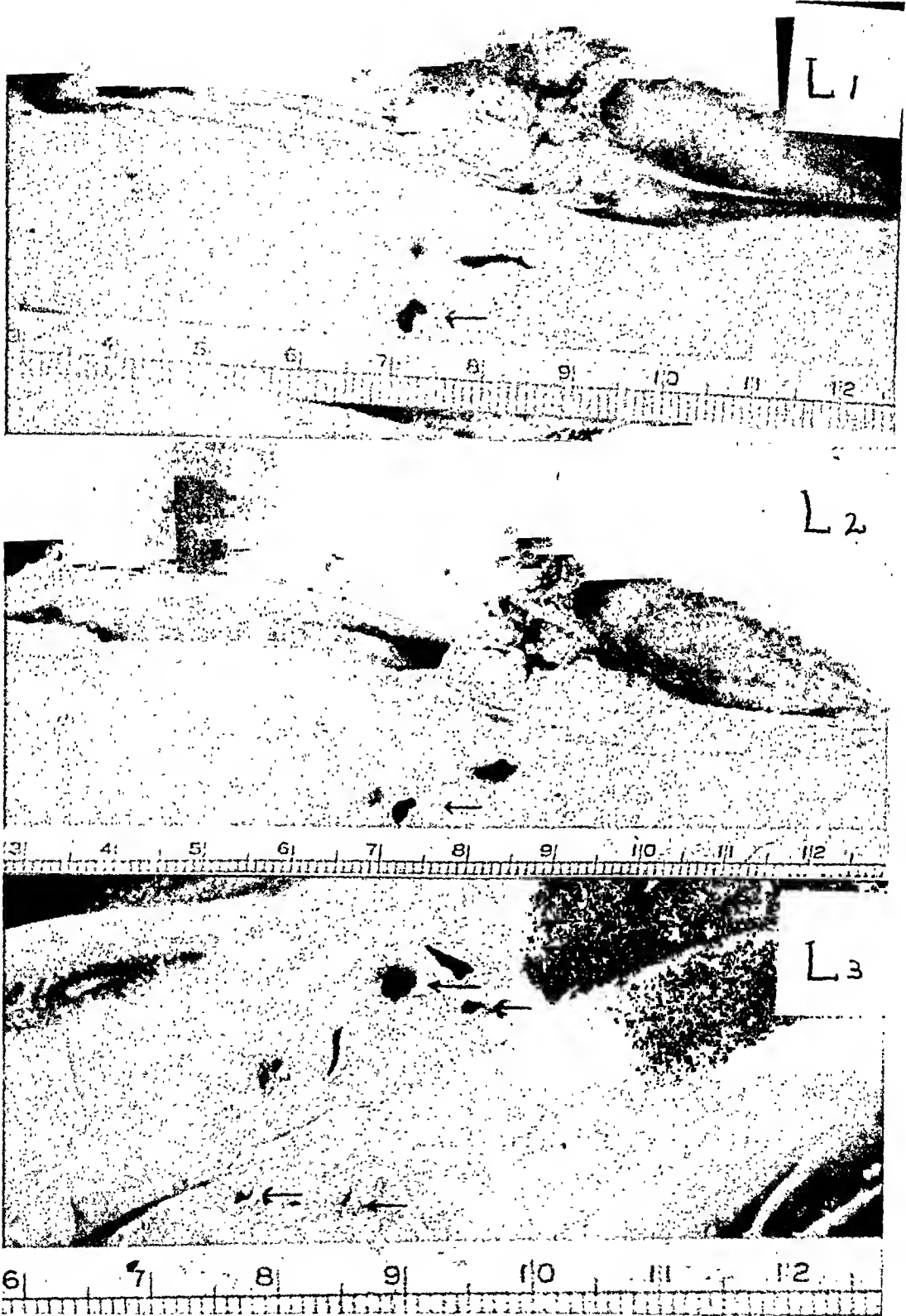
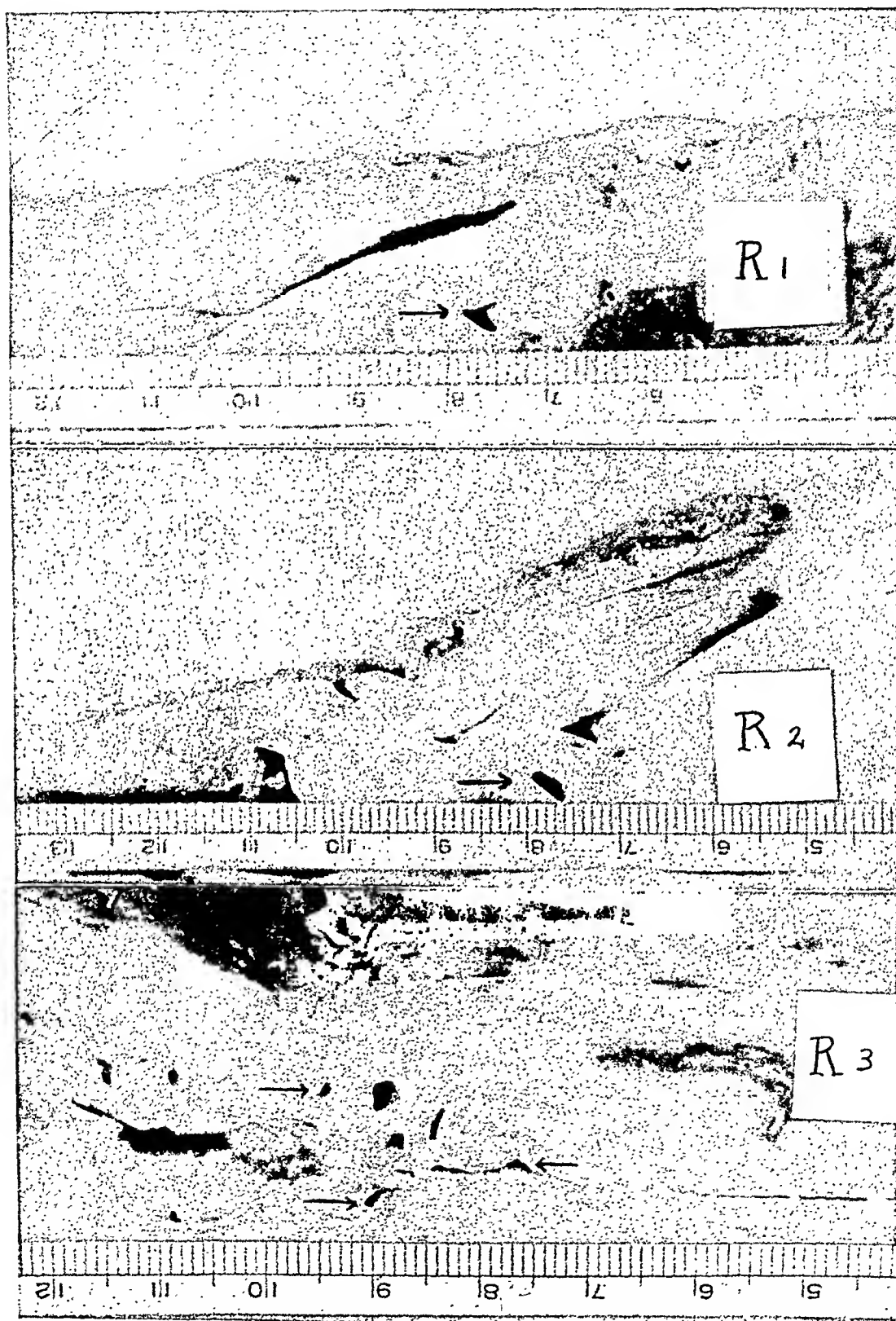


FIG. 2. Cross sections through the neoplastic mass showing compression of the renal arteries. The arrows in each picture point to the renal artery or its branches. The



identification number on each picture indicates the plane through the neoplasm as shown in figure 1.



FIG. 3. Section of kidney cortex showing hypertrophy of outer layer of Bowman's capsule in two glomeruli, atrophy of tubular epithelium, and infiltration of kidney substance with lymphoid cells. The lumina of the glomerular capillaries are devoid of blood.

the hypertension is only moderate in degree and is usually transient.<sup>2</sup> This contrasts with the severity of the hypertension produced by partial constriction of the renal arteries. The accompanying photographs clearly demonstrate that the renal arteries of the patient were definitely constricted.

It is interesting to note that the severity of the hypertension and the reduction of urea clearance closely paralleled the amount of edema in the lower extremities. This seems significant if it is an indication that the degree of constriction of the renal arteries varied with the degree of constriction of the aorta and vena cava. However, in dogs the degree of hypertension does not always increase with increased constriction of the renal arteries. Furthermore, hypertension can be produced by constriction of the renal arteries too slight to alter the renal clearances.<sup>3</sup>

### CONCLUSION

A patient with arterial hypertension was studied in whom the genesis of the hypertension was apparently due to partial constriction of the renal arteries simulating the production of experimental hypertension by the Goldblatt clamp.

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## HEMOLYTIC REACTION FOLLOWING BLOOD TRANSFUSION; REPORT OF A CASE OF INTRA-GROUP INCOMPATIBILITY \*

By HARRY MANDELBAUM, M.D., *Brooklyn, New York*

BEFORE the days of blood grouping, hemoglobinuria was a common sequel of blood transfusion, and in many of the cases renal insufficiency developed, usually with lethal termination. Such hemolytic transfusion reactions were first described by Denys<sup>1</sup> in 1667. Their frequent occurrence in his cases was not surprising, for he had been injecting sheep's blood into human beings. However, similar reactions occurred in a large percentage of the cases where human blood, exclusively, was transfused. This served as a barrier to the wide usage of blood transfusion as a therapeutic measure.

In 1900 and 1901, Landsteiner<sup>2</sup> showed that the serum of certain normal individuals can agglutinate or hemolyze the red blood cells of certain other normal individuals. On the basis of his studies, he was able to identify three

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From the Department of Medicine, the Jewish Hospital of Brooklyn.

distinct groups. The fourth blood group (AB) was described in 1902 by Decastello and Sturli,<sup>3</sup> the latter a pupil of Landsteiner.

When donors are selected according to their blood groups, blood transfusion is a relatively safe procedure. Where hemolytic reactions have occurred, in the vast majority of the cases errors in blood grouping have been responsible, as shown by Bordley.<sup>4</sup> The second most common cause of hemolytic reactions is the indiscriminate use of the so-called universal donor for recipients not belonging to group O. In a minority of the cases, hemolytic reactions have been traced to the presence of atypical agglutinins in the recipient's serum, which agglutinated the donor's red blood cells.<sup>5,6</sup> Such cases can be detected by cross-matching.

Therefore cross-matching has been added to blood grouping as the routine procedure in determining compatibility before transfusion. Despite these precautions, however, reports of hemolytic reactions, where careful blood grouping and cross-typing had been observed, continue to appear.<sup>7,8</sup> Fortunately such cases are rare. The unusual clinical features of such a case, recently seen, warrant a detailed report.

#### CASE REPORT

L. E. D., 38 years of age, was admitted in labor to the Jewish Hospital of Brooklyn \* May 24, 1937, and discharged July 24, 1937.

*Family history.* Her father had been treated for malignant hypertension for years, and died following a hemiplegia. Her mother was an advanced arteriosclerotic with hypertension.

*Past personal history.* There had been no illness, excepting influenza in 1918. There had been three pregnancies (1924, 1925 and 1935), each terminating prematurely in the seventh month. Hypertension complicated the last pregnancy (1935); the blood pressure reached 160 systolic and 106 diastolic; the urine was normal; the blood Wassermann test, normal; and blood chemical tests were reported as follows: Urea, 11.06 mg. per 100 c.c.; uric acid, 4.1 mg. per 100 c.c.; CO<sub>2</sub> combining power, 42.9 volumes per cent. A few days after delivery, her blood pressure returned to normal.

In November, 1936, she became pregnant. Her blood pressure was 180 systolic, 100 diastolic. During the succeeding months it ranged between 142/80 and 190/100. Frequent urine analyses revealed no abnormal findings. On April 13, 1937, because of increasing headaches and persistent hypertension, she was admitted to the hospital for further study. The physical examination disclosed nothing remarkable; the eye grounds were normal. Laboratory studies revealed the following data: There was no negative water balance; the kidneys diluted well and concentrated well (1.002 to 1.028). Phenolsulphonephthalein test showed that a total of 86.6 per cent of the dye was excreted in two hours, 68 per cent in the first hour. Non-protein nitrogen, 17.7 mg. per 100 c.c.; urea, 9.9 mg. per 100 c.c.; uric acid, 3.1 mg. per 100 c.c.; creatinine, 1.7 mg. per 100 c.c. The urea clearance was 112 per cent of normal the first hour, and 101 per cent of normal the second hour. The blood pressure was 198/112 on admission, rose to 210/130 the day following, then gradually declined, reaching 150/110 on the sixth day. Because of prematurity of each of her preceding pregnancies, it was decided not to interrupt this pregnancy.

*Present admission.* The patient went into labor at 4 p.m., May 24, 1937. Her blood pressure was 276/160. A male child was delivered at 11:15 p.m.

*May 25:* Blood continued to ooze from the vagina, her pulse rate rising steadily. At 4 a.m. she complained of weakness, the skin was cold and clammy, her pulse rapid

\* On the private service of Dr. S. G. Blum.

and of poor volume. She was returned to the operating room, and the uterus was explored; some decidua and blood clots were removed, and a tear in the cervix sutured. The patient was returned to her room in shock and a transfusion was ordered.

The patient's blood was grouped with standard sera of high potency and found to belong to group A; her husband's blood was also found to belong to group A; cross-matching was performed and the blood samples found to be compatible. A transfusion of 500 c.c. of blood was given by Dr. A. S. Wiener, by the direct method. No immediate reaction was observed during the transfusion. No chills or fever were noted after the transfusion. A continuous intravenous infusion of physiologic saline was given during the rest of the day. Her general condition remained unchanged.

*May 26:* The patient appeared somewhat better. She had not voided since delivery. At 4 p.m. (30 hours after the transfusion) three ounces of a turbid, dark red urine were obtained by catheterization. The blood pressure was 160/110.

*May 27:* The patient was very restless, the pulse was rapid and of small volume; pruritus was marked; small petechiae were found widely scattered over the body; the sclerae showed a slight icteric tint. At 4 a.m., catheterization yielded one half ounce of a turbid, dark red urine; at 4 p.m., none was obtained after catheterization. The blood pressure was 130/95.

*May 28:* The patient was drowsy, slight nuchal rigidity was evident, and coarse muscular twitchings were observed in all the extremities. The heart sounds were of better tone, the pulse rate was 96 and of better volume. Her blood pressure was 125/105. The liver was felt an inch below the costal border. There was tenderness in the right flank. The eye grounds were normal. Catheterization at 4 a.m. and at 4 p.m. yielded an ounce of turbid, dark red urine.

*May 29:* The patient was incoherent, pruritus was marked; icterus was evident in the skin and sclerae; the pupils were pin-point in size; the neck showed slight rigidity. Slight edema was evident over the face and extremities. The liver edge was felt three inches below the costal border. The right kidney was markedly enlarged and tender. Large purpuric areas appeared over the trunk and extremities. The patient voided four ounces of a turbid, dark red urine. The blood pressure was 235/140.

*May 30:* The patient was coherent. Rigidity of the neck was no longer demonstrable and the coarse muscle twitchings were only occasionally evident. The skin appeared more edematous; new crops of purpura were seen. The pruritus was intolerable. A soft, blowing systolic murmur was heard over the mitral area. The patient voided six ounces of a turbid, dark red urine. The icteric index was 23. Her blood pressure was 160/100.

*May 31:* At 3 p.m., the patient was seized with a paroxysm of coughing that lasted 15 minutes, followed by expectoration of blood-streaked sputum. The heart rate was accentuated, the sounds were of good quality; the mitral systolic appeared somewhat harsher than the day previously. The lungs showed nothing remarkable. Seven ounces of a turbid, brown-red urine were passed. The blood pressure was 195/130.

*June 1:* The skin appeared darker (bronzed) and more edematous; fresh crops of purpura appeared. The liver edge was felt two inches below the costal edge and was less tender. Ten ounces of a dark brown urine were passed. The blood pressure was 170/110.

*June 2:* Several areas of induration appeared over the lower back which caused the patient considerable pain. The pruritus continued a source of great discomfort. Nine ounces of dark amber urine were voided. The blood pressure was 160/105.

*June 3:* The skin was more edematous, the bronzing more distinct. A peri-

cardial friction rub was evident over the entire precordium. The lungs were clear. The liver was felt at the costal edge. The patient voided 10 ounces of turbid, dark amber urine. The blood pressure was 155/95.

*June 4:* The patient complained of severe precordial pain. Dyspnea was marked. The pericardial friction murmur persisted. Dullness and diminished breathing were noted over the left base and axilla. Nine ounces of urine were passed. The blood pressure was 155/95.

*June 5:* The edema of the skin was so marked that patient complained of "tightness of the skin"; it was decidedly bronzed, and the pruritus had not abated. The areas of induration over the lower back had formed into four large carbuncles. The pericardial friction sounds could be heard all over the precordium. An effusion had developed in the left chest, reaching to the angle of the scapula. Frequency of micturition was evident, and 30 ounces of urine were passed. The blood pressure was 150/95.

*June 6 and June 7:* There were no changes noted. The urinary excretion balanced the total fluid intake (1500 c.c.) The blood pressure was 130/85.

*June 8:* The skin appeared less edematous; the bronzing and the pruritus continued, unchanged. The pericardial friction murmur could be heard only toward the base of the heart. The pleural effusion had appreciably diminished. The carbuncles appeared larger. The total fluid intake was 1500 c.c.; the output, 1200 c.c. The blood pressure was 150/95.

*June 9:* The pericardial friction murmur was no longer evident and the effusion apparently had been completely absorbed. Diuresis was marked, the patient voiding 2400 c.c. of urine. The blood pressure was 160/112.

*June 10:* The edema was no longer evident. The bronzing of the skin was not as deep, but the pruritus continued, unabated. The intake was 1200 c.c., the output, 2700 c.c.

*June 11:* The icteric index was 5. The total fluid intake was 2100 c.c., the output 2500 c.c. The blood pressure was 140/95.

*June 12:* The skin appeared lighter; the pruritus continued unrelentingly. The systolic murmur heard over the mitral was decidedly louder and roughened. Central areas of softening appeared in the carbuncles. The total fluid intake was 1800 c.c., the output, 2000 c.c.

*June 13:* The carbuncles had begun to drain, status otherwise unchanged. Intake, 1600 c.c.; output, 1200 c.c.

*June 14 to June 23:* The skin gradually lost its pigmentation; the pruritus, however, continued, uninfluenced by therapy; the mitral systolic murmur persisted, loud and harsh; the water metabolism was well balanced; the carbuncles drained freely; the blood pressure remained at a level of 130/80.

*June 24:* Another carbuncle had developed at the base of the spine. At 4 p.m., the patient developed an attack of dyspnea, her skin became cold and clammy, and the pulse rapid and feeble. After a half hour, all symptoms had disappeared. There were no changes in the cardiac or pulmonary findings.

*June 25 to June 28:* The carbuncles were draining freely. The lungs were clear, the systolic murmur in the mitral area was loud and harsh. The water metabolism continued balanced, the blood pressure remained at the former level, the pruritus seemed to be less troublesome.

*June 29:* At noon, the patient had an attack similar to the one on June 24. The dyspnea, however, continued all day, and there were several paroxysms of coughing, with expectoration of blood-streaked sputum. The heart rate became somewhat accelerated; toward evening a few crepitant râles were heard over the base of the left lung.

*June 30:* Showers of crepitant râles were heard over the left base. In the after-



noon broncho-vesicular breathing was noted over the left base. In the evening, effusion of the left chest was evident, reaching to the angle of the left scapula.

*July 1:* The patient was not dyspneic or cyanotic; she coughed frequently with expectoration of non-odorous, green muco-pus. Flatness was obtained all over the left chest, anteriorly, posteriorly and in the axilla; the breath sounds were not heard. The heart was not displaced; the murmur heard over the mitral area was softer; the pulse rate was 96.

*July 2 to July 3:* The cough and expectoration were less marked. Roentgenogram of the chest revealed considerable fluid in the left chest, the heart not displaced and the right lung field clear.

*July 4:* Diagnostic thoracentesis; 60 c.c. of a cloudy, straw-colored fluid removed. Culture was subsequently reported negative. The fluid was rich in proteins and coagulated spontaneously on standing.

*July 5 to July 11:* The patient was comfortable, the pruritus was definitely improved. The pleural effusion gradually was absorbed. The heart was regular, of good quality and the soft systolic murmur over the mitral area persisted.

*July 12 to July 16:* Another carbuncle developed over the left buttock. This was incised on July 16.

*July 17 to July 24:* The patient out of bed. The heart was of normal size, a soft systolic murmur was present over the mitral area. The lungs were clear. All the carbuncles were draining freely. The blood pressure was 130/90.

*Subsequent course:* The patient has remained in good health since discharge from the hospital. The carbuncles did not completely heal until late in September. The kidneys concentrate well, the blood pressure ranges between 130/90 and 150/95, the soft mitral systolic has persisted.

*Summary of temperature record:* There was no chill or temperature elevation following the transfusion. The temperature did not rise above 100° until two weeks later. Then, with the appearance of the cardiac murmur and the carbuncles, it became remittent, never exceeding 103°. It continued, thus, from June 7 to July 15. After July 15, the peak of the temperature declined daily, reaching normal five days later.

*Summary of laboratory data.*

*Urine analyses.* The first specimen of urine, after delivery, was the three ounces obtained by catheterization 30 hours after transfusion. This was turbid, dark red, and showed the presence of free hemoglobin chemically and spectroscopically; no red blood cells or leukocytes were found. Free hemoglobin was detected in all subsequent samples until June 3. Red blood cells were first noted May 29, increased in amount up to June 3, then progressively decreased numerically and finally disappeared June 8. Leukocytes were first found in the urine on May 30, increased in number and were also reported in clumps, up to June 6, then became less numerous in subsequent specimens. The reaction of the urine was always alkaline. The specific gravity varied from 1.006 to 1.018.

*Blood and differential counts and hemoglobin determinations* are presented in figure 1 and table 1.

*Blood chemistry studies.* The extent of the azotemia is graphically shown in figure 1. It will be noted that the blood chemistry findings were normal one month before delivery. Following transfusion, there was an abrupt azotemia. The urea increased to 60.3 mg. per cent on May 27, mounted steadily to reach a peak of 215.5 mg. per cent on June 8, then gradually declined reaching 44.4 mg. per cent on September 4. The non-protein nitrogen curve paralleled the urea curve, reaching 262.2 mg. per cent on June 8, then gradually declined. The creatinine reached its peak of 16 mg. per cent on June 3, then gradually fell, reaching 3 mg. per cent on Sept. 4. The uric acid reached 21.9 mg. per cent on June 5, then steadily declined. The CO<sub>2</sub>



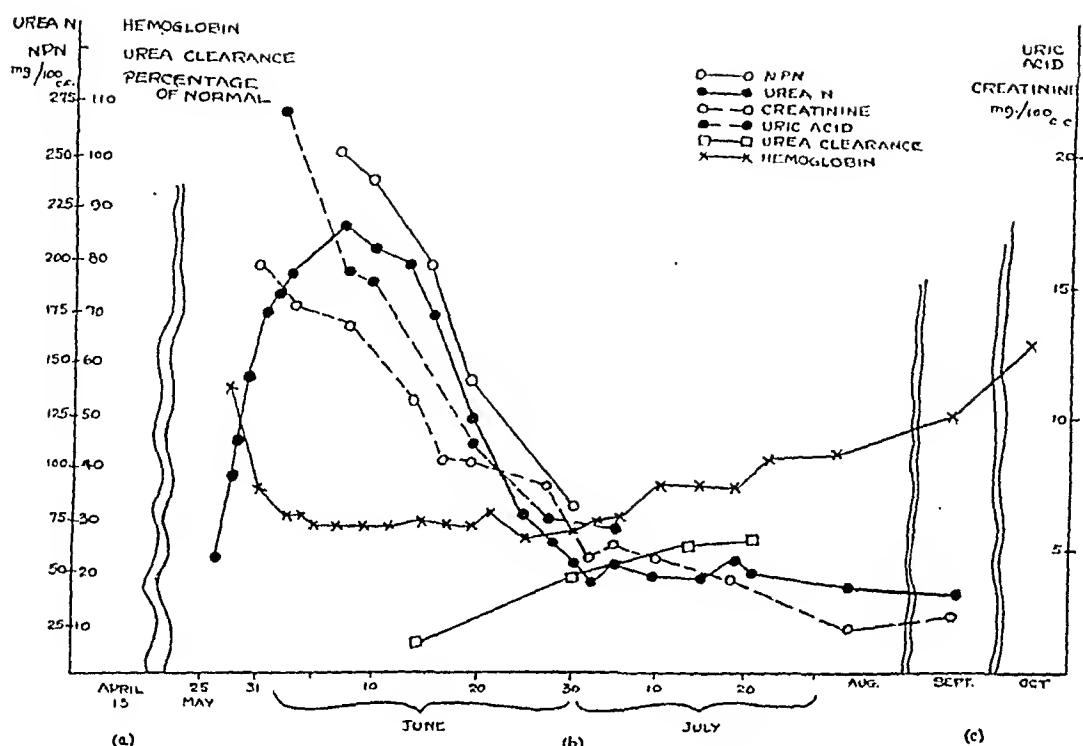


FIG. 1. The blood chemical studies: (a) during the period of the patient's stay in the hospital in April, all findings were normal; (b) during the period following the blood transfusion; and (c) after her discharge from the hospital.

TABLE I  
Blood and Differential Counts, and Hemoglobin Determinations

Date	R.B.C.	Hgb.	W.B.C.	Polys.	Eosin.	Bas.	Lymph.	Mono- cytes	Reticu- locyte
5-30	2,700,000	56%	32,900	84%	0%	0%	14%	2%	
6-1	2,200,000	37%	31,400	82%	0%	0%	18%	0%	
6-3	1,870,000	33%	33,000	92%	0%	0%	7%	1%	
6-4	1,780,000	33%							
6-5	1,330,000	30%	21,700	90%	0%	0%	9%	1%	
6-7	1,590,000	30%	25,950	96%	0%	0%	2%	2%	
6-9	1,510,000	30%	26,150	94%	0%	0%	6%	0%	
6-11	1,440,000	30%	29,350	95%	0%	0%	5%	0%	2.5%
6-14	1,850,000	31%	32,300	94%	0%	0%	6%	0%	5%
6-16	1,450,000	31%	29,900	97%	0%	0%	3%	0%	
6-18	1,640,000	31%	13,900	92%	0%	0%	8%	0%	1.6%
6-21	1,650,000	34%	11,500	90%	0%	1%	9%	0%	
6-25	1,330,000	29%	9,400	93%	0%	0%	7%	0%	
6-29	1,350,000	32%	11,750	80%	0%	0%	20%	0%	
7-2	1,990,000	34%	11,800	86%	0%	0%	14%	0%	
7-6	1,700,000	34%	9,300	84%	0%	0%	16%	0%	
7-10	2,500,000	40%	17,250	83%	1%	0%	16%	0%	
7-15	2,030,000	40%	9,100	74%	0%	0%	24%	2%	
7-19	2,580,000	40%	8,300	70%	2%	0%	24%	4%	
7-23	2,590,000	47%	9,550	76%	0%	0%	24%	0%	
8-2	3,210,000	49%	8,700	72%	0%	0%	25%	3%	
9-4	3,840,000	70%	7,600	74%	1%	1%	22%	2%	
10-2	4,240,000	76%	6,900	77%	1%	0%	22%	0%	

combining power was 34.2 volumes per cent on May 31, then ranged between 40.2 and 47.5 volumes per cent.

The urea clearance one month before delivery was 110 per cent of the average normal. On June 16 it was  $7\frac{1}{2}$  per cent, then slowly increased, reaching 25.5 per cent of normal on June 22.

The results of the determinations of blood proteins, as well as of the albumin and globulin fractions are shown in table 2.

TABLE II

Blood Protein Studies (in gm. per 100 c.c. of serum) During and Following the Period of Edema

Date	Total Protein	Alb.	Glob.	A/G Ratio
6-8	5.04	2.20	2.84	0.77
6-11	5.67	2.05	3.62	0.57
6-21	5.19	2.13	3.06	0.70
6-29	6.35	3.37	2.98	1.13

*Blood cultures.* No growth was reported on blood cultured on June 14, June 30 and July 2.

### DISCUSSION

In general the mortality due to blood transfusion varies in different clinics from 0.2 per cent to 1 per cent depending on the technic used. A good proportion of these deaths can be traced to hemolytic reactions with renal insufficiency. In most cases, symptoms become manifest during or immediately following the transfusion, viz., pain in the lumbar region, a cold, clammy sweat, a sense of constriction in the chest, and varying degrees of shock; chills and fever usually follow. Partial or complete suppression of urine, with hemoglobinemia and hemoglobinuria are characteristically present; itching and jaundice may become apparent within 48 hours, and in most cases, edema develops. With the suppression of renal function, clinical uremia appears, with increasing azotemia; (in Baker and Dodds' <sup>9</sup> case, the urea rose to 920 mg. per 100 c.c. and the creatinine to 26 mg. per 100 c.c.).

In the cases <sup>8, 9, 10</sup> that came to autopsy, the description of the basic pathology was similar. There was dilatation of the tubules caused by the plugging of the tubular system with a substance in the form of small masses and granules of varying size, that stained with eosin. The tubules showed a varying degree of degeneration of their epithelium, not unlike the picture of mercurial nephrosis. The convoluted tubules and Henle's loops were most frequently involved. In several cases, focal hepatic necrosis has been described.

### MECHANISM OF THE PRODUCTION OF SUPPRESSION OF RENAL FUNCTION

*The obstructive theory* has most advocates. DeGowin et al.,<sup>10</sup> by injecting solutions of hemoglobin into the blood of dogs, Yorke and Nauss<sup>11</sup> and Baker and Dodds<sup>9</sup> by similar experiments in rabbits, and Melnick et al.<sup>12</sup> by repeated infusions of red blood cells into dogs, reproduced the clinical and pathological picture of renal suppression due to obstruction of the tubules. They have shown that the kidney readily excretes hemoglobin as oxyhemoglobin when the reaction

of the urine is alkaline. When the reaction is acid, precipitation of the hemoglobin occurs with obstruction of the renal tubules. This precipitation was augmented in the presence of a concentration of sodium chloride above 1 per cent. Newman and Whipple<sup>13</sup> demonstrated the deposition of hemosiderin in the convoluted tubules of the kidney and in the liver, spleen and lymph nodes as well.

*Spasm of the Renal Vessels.* Mason and Mann<sup>14</sup> produced vasoconstriction of the renal arteries by intravenous injections of hemoglobin. Hesse and Filatov<sup>15</sup> obtained similar results and concluded that the spasm of the renal arteries accounted for the failure of renal function. They found that transfusion of compatible blood relaxed the spasm of the renal arteries and restored renal function.

When a hemolytic reaction has occurred, the possibility of an error in blood grouping must first be considered. Bordley<sup>4</sup> stressed the necessity of rechecking the blood grouping in such cases. In my case, when samples of blood from the patient and the donor, her husband, were examined before the transfusion, they were found to belong to group A and to be compatible on cross-matching. Three days after the transfusion, fresh blood specimens were taken from the donor and recipient and studied by Dr. A. S. Wiener.\* He confirmed their group A classification and found them compatible on cross-matching. He further found that while the donor belonged to sub-group A<sub>1</sub>, the recipient belonged to sub-group A<sub>2</sub>. It was his opinion, however, that although they belonged to different sub-groups, this was not sufficient to account for the hemolytic reaction, since he was unable to demonstrate any agglutinins or hemolysins in the patient's serum which could act on the donor's red blood cells, or vice versa. Evidently this is another instance of an in vivo incompatibility which could not have been predicted by any of the present in vitro tests.

My patient showed all the characteristics of a transfusion hemolytic reaction: a protracted period of shock, complete and incomplete suppression of urine and clinical uremia with marked azotemia. Free hemoglobin was found in the serum and urine, jaundice developed, the icterus index was increased and pruritus was marked. The edema that developed was of the nephrotic type, the blood showing the characteristic reversal of the A/G ratio (table 2).

There were several distinctive features of this case that warrant further discussion. (1) The lack of the immediate symptoms that characterize these hemolytic reactions was probably masked by the protraction of the initial shock. No chills or temperature elevation were evident. (2) Pruritus developed 48 hours after the transfusion, and continued unabated for several weeks, resistant to all therapeutic measures. (3) When the azotemia reached its peak, pericarditis developed, occasioned considerable pain in the chest and lasted several days. (4) A systolic murmur was heard over the mitral area on the sixth day. At first soft, of short duration and of slight intensity, it later became rough, louder and filled all of systole. Finally, it returned to its original character. The murmur was still evident six months later. (5) The three embolic pulmonary episodes were probably secondary to a non-septic thrombo-phlebitis. However, the presence of an endocardial lesion, the irregular temperature and

\* Dr. Wiener also tested the blood specimens for their properties, M and N, and found that both belonged to type MN.

the repeatedly negative blood cultures in the presence of embolism, suggest the possibility of a non-bacterial thrombotic type of endocarditis such as has been described by Gross and Friedberg<sup>16</sup>; the embolus, arising from its mitral seat, may have passed through one of the bronchial arteries to reach the lungs. (6) The purpuric eruption became widespread; the ecchymotic area over the lower back became the seat for the subsequent development of several carbuncles. The platelets at all times appeared adequately distributed over the blood smear. There was no bleeding from the mucous membranes such as occurs with the prothrombin or fibrinogen deficiency that characterizes anaphylactic reactions. The capillary endotheliotoxic action of some unknown retention product of uremia was probably the responsible cause. (7) The nephrotic picture resembled closely that of mercurial nephrosis. Erlanger<sup>17</sup> has shown that in the later stages of severe shock, the vessel walls become permeable to protein which, therefore, escapes from the blood into the extracellular spaces and transudates. (8) The distinct bronzing of the skin associated with hepatomegaly suggested widespread deposition of hemosiderin, as was experimentally shown by Newman and Whipple.<sup>13</sup>

*Treatment.* The protracted period of shock and the low hemoglobin and erythrocytic values raised the question of the advisability of giving another transfusion, using another donor (Hesse and Filatov<sup>15</sup>). However, when no assurance could be given the family that another reaction would not be summated on the other, further plans for such a procedure were abandoned. The anemia was treated by oral administrations of iron and parenteral liver extract.

The value of an alkaline urine had been established in the experimental animal. An alkaline urine favors the excretion of hemoglobin as oxyhemoglobin. Sodium bicarbonate in doses of 10 gr. four times daily was well tolerated by mouth and proved sufficient to keep the urine alkaline. The use of larger doses of alkalis may cause alkalosis in these patients, because of the lack of adjusting power of the kidneys (Peters,<sup>18</sup> Ellis<sup>19</sup>).

The great difficulty lies in reestablishing renal function. The routine adapted by Peters et al.<sup>20</sup> in the treatment of the anuria of mercurial nephrosis may readily be applied in these cases; to furnish adequate fluids (as physiologic saline) to provide a large urinary volume; to provide adequate nourishment to prevent starvation acidosis. Hypertonic glucose (50 c.c. of 50 per cent glucose) was given my patient intravenously twice daily for four days, together with 2000 c.c. of physiologic saline, parenterally. Then 4 grams daily of sodium chloride and 1500 c.c. of fluids were given orally, during the period of increasing edema. Diuresis was established on the eleventh day. No difficulty was encountered in maintaining an adequate carbohydrate and protein intake.

### SUMMARY

A case of hemolytic reaction following blood transfusion has been presented. The blood grouping and cross-matching before transfusion were carefully checked and found to be correct after transfusion. While both belonged to group A, with properties MN, the donor belonged to sub-group A<sub>1</sub> and the recipient to sub-group A<sub>2</sub>.

This case is another of those rare instances of in vivo incompatibility which could not have been prevented by any of the present in vitro tests.

The basis of treatment in this case was to establish an alkaline diuresis and maintain an adequate carbohydrate and protein intake.

*Note:* Since this case report was submitted, the patient was examined at regular intervals. Her recovery has been complete.

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## ANEURYSM OF THE AORTA WITH COMPRESSION OF THE SPINAL CORD; TWO CASE REPORTS AND REVIEW OF LITERATURE\*

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COMPRESSION of the spinal cord is a rare complication of syphilitic aortic aneurysm. Of the thousands of cases of aortic aneurysm that occur in the literature, only 44 present this syndrome. Laennec<sup>1</sup> in 1825 first described the clinical and the necropsy findings in a 36 year old man. In a thorough dissertation of the subject, Goldschmidt-Haas<sup>2</sup> in 1913 gathered and analyzed 32 cases. Gregory<sup>3</sup> in 1934 was able to assemble nine more, and three additional articles have appeared.<sup>4</sup>

The following two cases are presented because of the rarity of the condition. The 15 year survival in the first patient is unique, and the unilateral cord compression manifestations in the second patient are unusual.

### CASE REPORTS

*Case 1.* J. B., a 35-year-old negro ship-worker, was seen first on September 19, 1921, in the out-patient clinic of John Sealy Hospital. He complained of sharp, intermittent pain in the left side of his body, extending from the precordial to the lumbar region, of about a year's duration. The family history was irrelevant. He had married at the age of 18, and his wife had three still-births and a child that lived for 10 months; his second wife, when he was 32, bore a child that died when two months old. Physical examination at this time was normal except for a penile scar and a blood pressure of 145 mm. of mercury systolic and 105 diastolic. The blood Wassermann test was negative, but in October of the same year it was one plus.

The patient was in the hospital from June 9 to July 24, 1922 because of pain across the back and the left side of the chest, especially just beneath the left scapular angle; and because of tenderness to pressure along the sixth and seventh thoracic vertebrae, which he attributed to being hit by a crane a few days previously while working on a ship. There was an accentuated pulsation of the large vessels of the neck, and a faint systolic murmur at the aortic area. The remainder of the examination was negative; the patellar reflexes were normal and the Romberg test was negative. The urine had a faint trace of albumin and some hyaline and granular casts. Two Wassermann tests were reported three and one plus respectively. Roentgenographs of the chest showed no evidences of fracture, but there was an aneurysm of the transverse and the descending portions of the aortic arch, measuring 15 cm. in length, 10 cm. in width and 14.4 cm. transversely; the aorta was 10 cm. wide. No erosion of the vertebrae was noted. No treatment other than that for symptomatic relief was administered.

He returned to the clinic in September and October of 1922, stating that for several weeks he had had weakness of both legs and numbness of both feet. The patellar and achilles reflexes were found to be definitely exaggerated and the Romberg was positive. He was referred to the dermatology department, and although

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the record of the antisyphilitic therapy was missing, the patient was certain (in 1937) that at this time he received eight intravenous and 16 buttock injections at weekly intervals.

He was not seen again until April 19, 1926, when he was hospitalized until June 15, 1926. He had had to quit working because of the pain in the left side, which now was boring and constant in character. He had numbness of both feet, so that he could not sense on what he was walking, and weakness of his legs, requiring the use of a cane. Four months previously he had noted that lying down on the left side would make him cough and would produce a sensation of weight in his chest; the cough did not accentuate the back pain. A month before he had begun to have intermittent urinary incontinence. He had no dyspnea, dependent edema or other significant symptoms.

On physical examination, the heart was enlarged, measuring 10 cm. to the left of the midline, and there was a soft systolic murmur at the aortic area; the blood pressure in both arms was 120 systolic and 80 diastolic. The lungs were clear. The upper part of the body showed no neurological abnormalities. At the level of the seventh thoracic segment he was hyperesthetic to pin prick, and below that level sensation was reduced to pain, touch, heat and cold. The abdominal and cremasteric reflexes were absent. The patellar reflexes were equal and exaggerated, the Babinski sign was positive bilaterally, and there was clonus of both ankles. He could not stand without support and was recorded as being incontinent.

The urine was negative except for occasional faint traces of albumin. The red blood cell count was 4,200,000 with 70 per cent hemoglobin, and the white cell count was 6,000 with 61 per cent polymorphonuclears. The Wassermann test of the blood was negative. The cerebrospinal fluid was clear and colorless, with 10 lymphocytes, normal reducing properties, increase in the quantity of globulin, a negative Wassermann and a colloidal gold curve of 0000000000.

Fluoroscopy and roentgenography of the chest showed the left halves of the third, fourth, fifth and sixth thoracic vertebrae to be entirely destroyed by a large, round mass in the left chest, which also produced pressure and erosion of the posterior portions of the sixth and seventh ribs. The mass was continuous with the aortic shadow and of the same density as the heart; it was expansile and "in all probabilities an aneurysm of the aortic arch."

The next admission to the hospital was from April 14, 1927, to February 12, 1928. There were no significant changes in the history or the clinical findings except for some progression of the condition. The legs were spastic and he could walk only a few yards with the aid of crutches; he was incontinent. The level of hypesthesia remained at the seventh thoracic segment. The Wassermann test of the blood was negative, and the results of two examinations of the cerebrospinal fluid were the same as those obtained on previous study. Roentgenographs showed no increase in the erosion of the spine or in the size of the aneurysm.

A follow-up note in October 1928, stated that the patient was feeling well except for some pain in the back, and that he was confined to a wheel-chair.

Nine years later, in September 1937, he was seen in the streets of Galveston, propelling himself in a hand-driven wheel-chair, and was asked to reënter the hospital. Except for the pain in the back, still present on the left side, extending from the left scapula to the left groin, and the pain in the soles of both feet of the paraplegic legs, he felt well. He was incontinent, but could predict the times of his defecations and micturitions, and rarely soiled himself. He felt cold and dead from the waist down, but had had no trophic ulcers. He had no cough, dyspnea or precordial pain, although anger sometimes precipitated an uncomfortable cardiac palpitation and "heaviness in the chest." Constipation was troublesome, but his appetite was excellent and he had gained about 10 pounds in weight.

Physical examination at this time showed a negro, 51 years of age; he looked well except for the moderate atrophy of the lower extremities. His weight was about 200 pounds, and his height six feet. The temperature and the respiratory rate were normal, and the pulse rate 90 per minute. The head was normal except for some dental caries and the presence of arcus senilis; the pupils were small, regular and reacted to light and accommodation. The fundi were normal. There was a slight tracheal tug, and slight suprasternal pulsation. The left side of the chest appeared fuller than the right anteriorly, and a pulsation synchronous with the heart could be felt on firm pressure just to the left of the fifth thoracic vertebra. The left chest was dull to percussion and the breath and voice sounds were hardly audible except at the base posteriorly; the right lung was normal. The heart was enlarged, measuring 11 cm. to the left of the midline; the sounds were normal, with a soft systolic murmur at the aortic area. The blood pressure was 144 systolic and 110 diastolic in both arms; it could not be obtained in the lower extremities, where the pulse also was absent. The arms were normal; the fingers were not clubbed. The abdomen was obese and normal. The back was stiff and tender to pressure on the fourth to the seventh thoracic vertebrae; no masses or deformities were visible. There was moderate atrophy of the musculature of the lower extremities and well-developed foot-drop. The skin below the seventh thoracic segment was drier and less resilient to the pinch than the integument above the level. This was also the line for marked hypesthesia to pin-prick and anesthesia to light touch. He could move the toes slightly and was able to contract feebly the adductor muscles of the thigh. The legs were flaccid, but the patellar and achilles reflexes were markedly exaggerated, there were bilateral Babinsky, Gordon and Oppenheim signs, and sustained clonus of the ankles and the knees. The abdominal and the cremasteric reflexes were not elicited. The sense of position was present in the toes, and the vibratory sense was not impaired.

Urine examinations were negative; there were occasional pus cells in the sediment. The red blood cell counts ranged about 5,000,000 with 90 per cent hemoglobin, and the white counts about 9,000 with 70 per cent polymorphonuclears. The blood Wassermann and Eagle tests were negative. The sedimentation rate was 26 mm. in one hour. The blood urea was 22.4 mg. per cent and the non-protein nitrogen was 45.6 mg. per cent.

The electrocardiogram showed sinus tachycardia and sinus arrhythmia, ventricular premature contractions and left axis deviation (figure 1).

Fluoroscopic and roentgenographic studies indicated a massive aneurysm of the transverse and descending portions of the aortic arch. The mass measured 13.5 cm. in the transverse diameter and 13.5 cm. in the vertical and antero-posterior planes. There was extensive erosion of the fifth, sixth and seventh ribs and the third to the seventh thoracic vertebrae on the left side. The erosion of the spine in the two middle vertebrae extended approximately two-thirds across the segments, but the destruction on the anterior surfaces was very slight as compared to that on the lateral aspects. The mass was expansile at its lower margins and little if any in the upper and lateral sides, indicating that laminated clots were present; there was calcification just inside the aneurysmal wall in the upper and lateral borders (figure 2 a).

Lumbar puncture revealed the cerebrospinal fluid to be under a pressure of 170 mm. of water, and no rise in this pressure was elicited by jugular compression. There were three lymphocytes per cu. mm., and 45 mg. of protein; the Wassermann test was negative and the colloidal gold curve was 1111233321. Iodized oil injected intrathecally in the lumbar region demonstrated the block at the seventh thoracic segment (figure 2 b).

A day after the last procedure it was noted that the reflexes of the lower extremity were hypoactive, that the clonus had disappeared and that the pathological reflexes could not be demonstrated. These changes disappeared gradually, and five days later the neurological findings returned to the former status.



The patient is doing well, is capable of as much activity as his paralysis will permit, and his morale is excellent. Except for the history of eight intravenous and 16 intramuscular injections in 1923, and a few doses of potassium iodide, he has received no antisyphilitic treatment.

*Case 2.* F. J. H., a 54-year-old white night-watchman, was admitted to John Sealy Hospital on October 5, 1935, with the complaints of severe pain in the chest of two years' duration; of pain in the low back, left hip and thigh; and of difficulty in urination for 10 months.

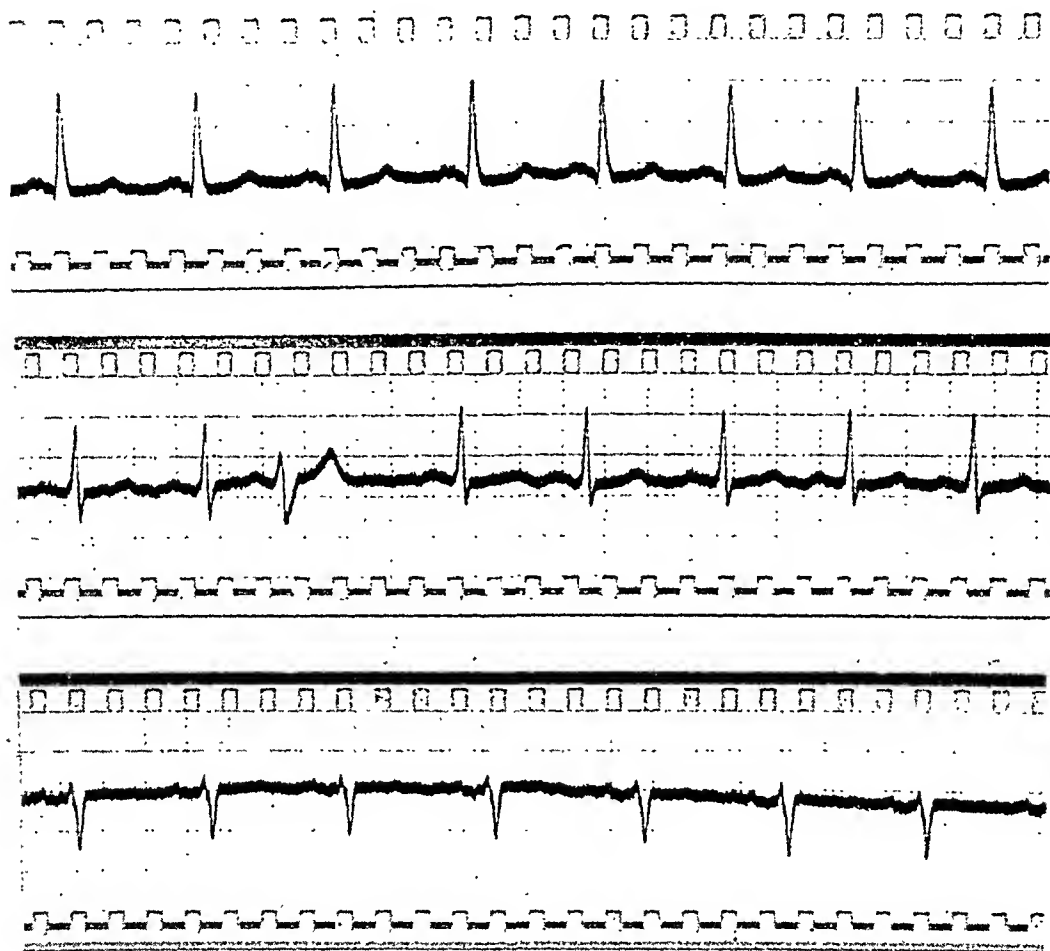


FIG. 1. Electrocardiogram in Case 1.

He had had two previous entries to the hospital. In 1934 he had acute gangrenous appendicitis, and was discharged 20 days post-operatively. In May 1935, he was on the urological service for acute urinary retention. At that time the heart was enlarged to 10.5 cm. to the left of the midline, the second aortic sound was accentuated and of tambour quality, and the blood pressure was 140 systolic and 90 diastolic. He had generalized abdominal pain and tenderness, with radiation down the thighs and into the scrotum. The urine was normal, the red blood cell count was 4,250,000 with 85 per cent hemoglobin, and the white blood cell count was 8,400 with 7.9 per cent polymorphonuclears. Cystoscopy revealed hypertrophy and trabecula-

tion of the bladder and prostatic enlargement. He was discharged with the diagnoses of chronic prostatitis and arteriosclerotic heart disease.

The man admitted a penile sore in 1915. He stated that he had noted some dyspnea on exertion since an attack of pneumonia in 1927. In 1932 he had begun to have intermittent attacks of severe pain in the left side of the chest, sharp and shooting in character, accentuated with deep respirations and on coughing, and located just under the breast but with occasional radiation to the right lower chest and back.



FIG. 2. a. Roentgenograph in Case 1, showing aneurysm and vertebral erosion.

During the previous two years his dyspnea had progressed so that he could walk only two blocks without resting. In January 1935, he began to notice difficulty in initiating micturition, and some dribbling of urine. He also began to have pain in the lumbar region of the back, which radiated to the left thigh and hip. At first this pain was paroxysmal, throbbing and "like a toothache;" it became progressively worse and finally constant, and during the two preceding weeks had involved the left lower portion of the abdomen.

The family history was irrelevant; he had six apparently healthy children. The past history was not significant except for a gradual loss of 70 pounds in weight and a resultant loss of strength during the preceding year.

Physical examination showed an elderly, emaciated man, weighing 110 pounds. The temperature was 99° F., the pulse rate was 85 per minute and the respiratory rate 22 per minute. The cervical, inguinal and epitrochlear lymph nodes were palpable. The left eye was almost blind because of an old traumatic corneal ulcer; the right



FIG. 2. b. Roentgenograph in Case 1, showing block of intrathecal iodized oil.

pupil was small, irregular and reacted sluggishly to light. The fundi were normal. There was impaired resonance at the base of the left lung posteriorly, and a few moist râles were heard in that area. The heart was enlarged to 11 cm. to the left of the midline. The rate and rhythm were normal, there were systolic murmurs at the aortic and mitral areas, and a markedly accentuated second aortic sound; the blood pressure was 134 systolic and 74 diastolic in both arms. Examination of the abdomen revealed a visible pulsation on the left side, and a pulsating mass was felt in the left upper quadrant, which was thought to be an aneurysm of the abdominal aorta. He was

tender to pressure on the abdomen and had slight rigidity of the upper abdominal muscles. The left elbow was ankylosed from an old injury. The left leg felt much warmer than the right, but there was no edema, and the peripheral pulses were good and equal in both lower extremities.

He swayed to the left on walking. The left gluteal muscles were atrophied, and the muscle power of the left leg was decreased. The achilles reflex was absent on the left and present on the right, but the other deep reflexes were normal; there was a suggestive Babinsky sign on the left side. Hypesthesia to pain and pressure was detected on the left side below the sixth thoracic segment; sensation on the right side of the body was normal. Rectal examination revealed relaxation of the anal sphincter and an enlarged prostate. He was noted to be incontinent.

The urine had a slight trace of albumin, many red blood cells and a few pus cells. The red blood count was 3,600,000 with 60 per cent hemoglobin, and the white blood cell count varied between 7,600 and 13,000, with about 80 per cent polymorphonuclears. The Wassermann test was two plus and the Eagle test was positive. Nonprotein nitrogen of the blood was 28.5 mg. per cent, and the urea nitrogen 17.1 mg. per cent a few days after admission.

Lumbar puncture was performed on October 11, 1935; the fluid was clear, with 10 mg. of protein and no cells, with a negative Wassermann test and a colloidal gold curve of 1232100000. The initial pressure was 320 mm. of water, with a prompt rise to 560 mm. and a prompt fall to 320 mm. of water upon jugular compression. Seven days later, the fluid was clear, with 19 mg. of protein, normal reducing properties, 1 lymphocyte, anticomplementary Wassermann test and a colloidal gold curve of 1223100000.

Antero-posterior and lateral roentgenographs of the lower spine visualized extensive destruction of the thoracic eleventh and twelfth and the lumbar first and second vertebrae; the erosion was principally on the anterior aspect, but also involved the left sides of the bones. It was interpreted as being due to an aneurysm of the abdominal aorta.

The patient's course in the hospital was steadily down-hill. He had occasional elevations of temperature up to 102° F., a pulse rate of 80 to 100 per minute and a normal respiratory rate. The pain in the lumbar region of the back and the left leg became progressively worse.

Examination of the chest on November 11, 1935, revealed decreased expansion of the left side, dullness on percussion, absent tactile fremitus, absent breath sounds and no transmission of the spoken voice; the heart was displaced to the right and Grocco's triangle was made out posteriorly on the right side. Roentgenographs of the chest showed dense opacity of the left chest and displacement of the heart shadow, indicative of massive effusion. Five hundred cubic centimeters of bloody fluid were aspirated; the specific gravity of the fluid was 1.027; and numerous red blood cells, 1,300 leukocytes and no organisms were found microscopically. Another 500 c.c. of blood were removed from the left pleural cavity on November 18, 1935, but the fluid reaccumulated rapidly and no further thoracenteses were done.

Early in December slight pitting edema of the ankles was observed, and there was transient swelling of the left, and then of the right, arm. On December 14, the left leg was completely anesthetic, the deep reflexes were absent and the Babinsky sign was positive; the right leg was normal. The breath was markedly urinous in odor, the heart sounds were rapid and of poor quality, and the right lung base contained moist râles; the left pleural cavity had the physical signs of massive effusion. The patient continued to have pain in the left chest, swelling of the left arm and some difficulty in swallowing. On January 3, 1936, he began to vomit, gradually became stuporous, and expired on January 6, 1936.

Treatment had been directed chiefly towards the relief of pain; potassium iodide, up to 0.3 gm. three times a day, was given, and between November 23 and

December 14, 1935, he received 19 doses of mercury succinamide, 0.01 gm. intramuscularly.

*Necropsy.* Necropsy was performed 36 hours after death.

The left pleural cavity contained about 1200 c.c. of blood, much of it in the form of fairly firm clots, and in the right chest there were about 150 c.c. of bloody fluid. The pericardial and the peritoneal cavities were normal. The heart weighed 380 gm., and was normal except for hypertrophy of the left ventricle; the aortic valves were normal.

The ascending aorta measured 6 cm. in the internal diameter; the intima had many small yellow plaques and tree-bark striations. Just at the origin of the left subclavian artery the aorta was dilated to 17 cm. in diameter; this dilatation extended fairly evenly down to the second lumbar segment: the greatest diameter of 20 cm. was at the seventh thoracic region and there were constrictions to 15 cm. at the fifth thoracic and at the diaphragmatic opening. In the middle of this tri-lobar aortic dilatation, on the posterior aspect, was an oval aneurysmal sac, measuring 7 cm. in the vertical and 3.5 cm. in the horizontal planes, and lying opposite the seventh and portions of the sixth and eighth thoracic vertebrae. There was some erosion of the vertebrae on the anterior and left lateral aspects of the fifth thoracic to the second lumbar segments, but the oval sacculatation had destroyed the anterior and the left lateral surfaces of the bones and produced direct pressure on the cord at the level of the sixth to the eighth thoracic vertebrae. The wall of the aneurysm adhered firmly to the bone and the dura, and around the attachment to the vertebral bodies leakage of blood had occurred, with extension of blood into the left pleural cavity and the left retroperitoneal region. No definite rupture of the aorta was found. There was no blood around the spinal cord, and the spine had no pathological fracture. The wall of the whole descending aorta, especially on the posterior surface at the level of the fifth to the eighth thoracic vertebrae, was thin and the layers of the vessel wall were indistinguishable. The intima contained many soft yellow plaques and vertical tree-bark striations.

The remainder of the findings were not significant. There was congestion of the liver and the lungs, the mucosa of the bladder was red and injected, and the prostate was enlarged.

Microscopic sections of the aorta showed perivascular infiltration by lymphocytes and changes in the wall diagnostic of syphilis. The arterioles and the arteries of the kidneys were thickened, and the bladder was chronically inflamed. Unfortunately, no detailed studies were made of the spinal cord.

## DISCUSSION

All of the aneurysms of the aorta producing spinal cord compression reported in the literature, as far as can be determined from the clinical, the serological or the pathological findings, were of syphilitic origin. In view of the frequency in which aortic aneurysms erode the vertebrae, the occurrence of spinal cord involvement is rare. Lucke and Rea,<sup>5</sup> in a study of 249 subjects, tabulated such erosion in 53, and spinal cord compression only in one. An analysis of 100 aneurysms at John Sealy Hospital<sup>6</sup> showed that over a quarter erode the vertebrae to some degree; yet of 170 aneurysms only one involved the cord (Case 2).

The pathological process is that of gradual pressure-erosion of the contiguous structures by a large, long-standing aneurysmal tumor. Any portion of the aorta may be involved, although in the great majority of cases the aneurysm naturally arose in the descending thoracic aorta; in 44 cases the locations were distributed as follows: 33 in the descending thoracic aorta, six at the arch, four in the ab-

dominal and one in the ascending portion. The condition prior to actual cord compression is illustrated by eight cases collected by Goldschmidt-Haas<sup>2</sup> in which the aneurysm eroded an opening into the vertebral canal without actually involving the cord. The compression and the resultant peripheral symptoms may be due to any one of the three occurrences: the aneurysm may produce direct pressure on the cord; an epidural hemorrhage due to rupture of the aneurysmal sac may result; or the weakened bone structure may collapse and pinch off the cord. It is interesting that although cases of marked adhesion between the dura and the aneurysmal wall are reported, in no instance was the dura penetrated. The changes in the cord were secondary to pressure, and the pathological studies in cases with paraplegia varied from lack of grossly or microscopically demonstrable damage<sup>7</sup> to evidence of complete transverse myelitis. Concomitant neurosyphilitic involvement, such as *tabes dorsalis*<sup>8</sup> also has been described.

Many more males than females were reported with this syndrome; of 39 cases, only six were women. The youngest patient recorded was 30 years of age, and the oldest 79; the age distribution was as follows: third decade, 12; fourth decade, nine; fifth decade, 15; older, three. However, of the 26 cases occurring prior to 1913, 11 were in the third decade of life, whereas only one of the 13 subsequent cases was under 40 years of age. Antisyphilitic treatment was lacking or inadequate in all patients.

In the majority of cases in which the clinical history was given, symptoms of aneurysm—such as pain in the chest, dyspnea or cough—were present, often of several years' duration, before the manifestations of spinal cord involvement. The onset of the cord symptoms usually was gradual (in 22 of Goldschmidt-Haas' 32 cases), but sometimes was very sudden, especially when due to epidural hemorrhage or to pathological fracture of the spine.

Physical examination of the patients often revealed syphilitic stigmata, aortic regurgitation, or the classical signs of aneurysm. Pulsating tumors or deformity of the spine<sup>4b</sup> occasionally were encountered. The paraplegia differed in no respects from paraplegia due to other causes. In most instances the process was not complete and was spastic in type (Case 1). Preëxisting neurosyphilis confused the picture in several patients.<sup>8</sup> Unilateral involvement occurred (Case 2); and a Brown-Sequard syndrome was present in one patient.<sup>9</sup>

The variability in the results of the serological tests for syphilis in these patients is well illustrated in Case 1. Negative Wassermann tests were not uncommon.<sup>10</sup> In the cerebrospinal fluid, the cell count and the protein varied from normal to moderately elevated, and with epidural hemorrhage the fluid was blood-tinged; Froin's syndrome was reported,<sup>11</sup> but not consistently. In the more recent cases, spinal block was demonstrated by the hydrodynamics, either by jugular compression or by combined cisternal-lumbar puncture,<sup>3</sup> or by the intrathecal introduction of iodized oil. The fluid was normal in all respects in one patient,<sup>12</sup> but the block at the fourth thoracic segment was demonstrated by the latter method. As in Case 2, the involvement may not be sufficiently advanced to produce spinal canal block. Alterations in the fluid due to neurosyphilis also were found in several cases.

Roentgenographs cannot fail to show the large aneurysms and the marked destruction of the vertebrae in these cases; however, the importance of fluoro-

scopy must be stressed in the differentiation of aneurysms from other thoracic or abdominal tumors, such as neoplasms, echinococcus cysts and dermoids.

The diagnosis is based on the clinical picture of aneurysm, on the presence of paraplegia, and on the roentgenographic substantiation. The most important condition that enters into the differential diagnosis is cord tumor; a complete clinical and roentgenographical study should eliminate the possible confusion. It has been alluded to above that other tumors may erode the vertebrae and possibly cause compression of the cord. Paraplegia in a syphilitic may be due to a specific meningo-myelitis.<sup>13</sup> Dissecting aneurysm of the aorta may produce neurological phenomena secondary to the disturbances in the blood supply to the cord.<sup>14</sup> Furthermore, radicular symptoms are not infrequent in saccular aneurysms of the aorta, and may be mistaken for true spinal cord compression. For example, a 40-year-old negro, who died at John Sealy Hospital in July 1935, came in with pain, tenderness and rigidity of the abdomen; on operation a liter of blood was found, and ruptured aortic aneurysm was suspected. The man developed anesthesia and paralysis of the right leg two days before exitus, and roentgenographs revealed erosion of the first and second lumbar vertebrae. On necropsy there was a large ruptured aneurysm 9 cm. above the bifurcation of the aorta, with erosion of the first and second lumbar vertebrae, but no penetration into the spinal canal.

Treatment of patients with cord compression due to aortic aneurysm must be directed towards the preservation of the weakened bony framework by bed rest and applicable splinting. Laminectomy was tried in one instance,<sup>15</sup> with the predictable results. In regard to antisyphilitic therapy, Gregory's statement<sup>3</sup> that it "has been consistently unsuccessful" in these cases is not surprising considering the advanced nature of the process. Such treatment must be carried out with extreme care; the danger of the initial use of arsenicals is illustrated strikingly by one patient who died 10 hours after the injection of 0.15 gm. of neoarsphenamine.<sup>11</sup> As in other aneurysms of syphilitic etiology, gradually increased doses of heavy metals (e.g., bismuth salicylate, up to 0.1 gm.), weekly over a two to three month period, must be administered before starting neoarsphenamine, the initial injections of which should be in 0.025 to 0.05 gm. doses, gradually advanced to 0.3 gm. Arsenicals should be employed in courses of from 10 to 12 injections alternating between succeeding courses of bismuth or mercury. Potassium iodide may accompany this routine. "Thereafter, much will depend on the symptoms and on the response to treatment."<sup>16</sup>

The course and the prognosis of all aortic aneurysms are extremely variable. The majority of the patients die within a two-year period, but Cole and his co-workers<sup>16</sup> write that "the average duration of life after detection of aneurysm of patients who had only an inadequate treatment was 37 months, which increased to 75 months when adequate antisyphilitic treatment was given." Longevity is not rare, and survival with aortic aneurysm for as long as 29 years has been reported.<sup>17</sup> The duration of life in patients with spinal cord compression due to aortic aneurysm, from the first symptoms of aneurysm until death, was most often from two to three years, but a fatal outcome was usual within a few months—or acutely—after the onset of spinal cord involvement. The presence of the syndrome for 15 years (Case 1) is by far the longest on record.

## SUMMARY

1. Two reports are presented of syphilitic aneurysm of the aorta with erosion of the vertebrae and compression of the spinal cord; one patient has survived the condition for 15 years.

2. The clinical and the pathological findings, the treatment and the prognosis in aortic aneurysm with spinal cord compression, based on the review of 46 recorded cases, are discussed.

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## EDITORIAL

### *SYNTHETIC ESTROGENS*

The remarkable advances in the field of the chemotherapy of infectious diseases during the past two years have served somewhat to obscure the hardly less remarkable achievements, chiefly of English workers, in the field of synthetic substitutes for the female sex hormones. The essential point is the establishment of the fact that estrogenic activity is not exclusively a property of compounds structurally similar to the natural hormones, that is, possessing the phenanthrene nucleus. In a series of brilliant papers, Dodds and his co-workers at the Courtauld Institute in London have described a number of simpler substances having estrogenic properties and in some cases of even greater activity than the naturally occurring hormones or their derivatives.

The story of this discovery furnishes an example of an important advance which has emerged out of efforts originally directed toward quite a different goal, namely, the investigation of the possible relation between chemical structure and physiological action of carcinogenic agents. In 1933, Cook and Dodds, and their co-workers, described synthetic phenanthrene derivatives having estrogenic properties. They found many, including ergosterol and calciferol, as well as several which were also active carcinogens. Three years later (1936) Dodds reported a series of compounds, also active, which did not possess this phenanthrene condensed-ring structure. A certain degree of unsaturation appeared to be requisite, especially ethylenic bonds. Just two years ago Dodds made the announcement that a comparatively simple compound, anol, or *p*-hydroxy propenyl benzene, possessed a very high degree of estrogenic activity, although shortly afterwards he reported that the activity was not due to anol itself but to another substance separating from the mother liquor. It now seems quite clear that there are a number of active compounds which may be looked upon as simple condensation derivatives of anol, and related to stilbene. The most promising of these new synthetic compounds is 4:4' dihydroxy  $\alpha\beta$  diethyl stilbene, which Dodds has named stilboestrol. Stilboestrol appears to possess many, if not most, of the physiological and clinical properties of the natural hormone. Estrone effects in rodents have now been reported on the vagina, uterus, breasts, anterior pituitary, male sex organs, and on the sex behavior. Oral administration interrupts early pregnancy in rabbits. Recent clinical studies show that the compound may produce an estrone effect on the hypoplastic uterus. It will restore the normal functioning appearance to the atrophic (climacteric) vulva and vagina, may induce painful swelling of the breast, and will relieve in many cases the pain of dysmenorrhea. The restoration of genuine menstruation has also been reported in a castrate woman by the use of stilboestrol followed by progesterone. The two interesting thera-

peutic uses of the estrogens not directly related to sex function which have been found recently, namely, in the gonorrheal vaginitis of childhood and the relief of atrophic rhinitis, also seem to be equally influenced.

As Dodds and his co-workers have pointed out, the formula of stilboestrol can be written so that it has a resemblance to that of estrone but without the ring structure. The suggestion therefore arises as to whether stilboesterol, or a closely related compound, may represent either a building stone or a decomposition product of the naturally occurring estrogen. Since synthetic stilboestrol is active in ovariectomized animals, the possibility that it represents a breakdown product seems unlikely. It is remarkable indeed that such complicated physiological transformations can be brought about by such rather simple compounds.

The stilbene derivatives are not the only compounds with estrogenic action which have recently been studied. Robson and his co-workers at Edinburgh over a year ago described triphenyl ethylene, 10 mg. of which produced the typical estrus activity, including mating, in rodents for a continuous period of eight or nine weeks. When large subcutaneous doses of a closely related compound, triphenyl chlor-ethylene, were tested a more prolonged action resulted, in equivalent doses, than is obtained with the best of the estrogenic compounds in common use.

Recently there has been great interest, especially in England and in Germany, in the clinical possibilities of these new compounds, and particularly of stilboestrol and its simple derivatives. These can be rather easily prepared, and a rather extensive study, both on the Continent and by the Therapeutic Trials Committee of the Medical Research Council in England, seems to indicate their essential lack of toxicity. Certain side reactions, however, most serious of which are the occasional occurrence of rather severe nausea and vomiting, make it imperative that they be introduced into clinical use with great caution.

Of interest for future work is the possibility that this successful production of synthetic compounds with estrogenic activity may point the way to a search for substitutes for other hormones which also possess the phenanthrene grouping, such as progesterone, testosterone, and the cortical hormone. Although many theoretical objections may be proposed against the probable successful outcome of such efforts, the possibilities nevertheless remain and will no doubt be carefully explored.

G. H.

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*Erratum.* In Dr. Frederick M. Allen's article on "Tolerance and Toxicity of Insulin. II. With Forced Administration of Carbohydrate," February 1939 *ANNALS*, page 1271, the first sentence of the last paragraph should read: "The 14 kg. animal depicted in figure 2 survived an insulin dose of 2,000 units (in the *Physiatric Institute*)."

## REVIEWS

*Spinal Anesthesia.* By LOUIS H. MAXSON, A.B., M.D., Practicing Specialist in Anesthetics; Former Chief Anesthetist, Harborview (King County) Hospital, Seattle, Washington; with a foreword by W. WAYNE BABCOCK, M.D., LL.D., F.A.C.S., Professor of Surgery, Temple University School of Medicine. 409 pages; 16 × 23.5 cm. J. B. Lippincott Company, Philadelphia. 1938. Price, \$6.50.

Spinal anesthesia is a form of regional anesthesia, applicable to a relatively large portion of the body. Although it was discovered by Bier, a German, the method was first popularized by Tuffier and Reclus, two Frenchmen. In 1898, Bier had the temerity to have 2 c.c. of a 1 per cent cocaine solution (20 mg.) injected into his own spinal canal to observe its effects. Following this successful experiment, Bier administered a similar dose to his assistant, Schmeiden. In 1899, he reported six operations under low spinal anesthesia. Tait and Coglieri of San Francisco, apparently were the first surgeons in this country to make use of this method of anesthesia. Since Bier's discovery, there have been alternating waves of popularity and distrust of this method of anesthesia. George P. Pitkin probably stimulated the most widespread interest (1927) in spinal anesthesia and established it on a sound basis.

The author gives a detailed anatomical description of the vertebral column and spinal cord relationship. The influence of position on curve is considered. There is an excellent description of the autonomic or vegetative nervous system with its physiological divisions; and full data on the cerebro-spinal fluid.

The variables of spinal anesthesia are discussed. The various drugs which have been employed and their relative merits are dealt with. Pre-anesthetic medications are reviewed.

A chapter is devoted to technical considerations and another to technical difficulties with a review of typical technics from 1902 (Le Filliatre) to 1934 (Vehrs). The newer preparations are discussed, e.g. pontocaine, nupercaine, spinocaine, etc.

The effects of spinal anesthesia are described, both immediate and delayed. The causes of failures are considered, along with the difficulties, dangers and mortality. Complications and sequelae are discussed in detail. Space is devoted to comparison of the advantages and disadvantages of this method of anesthesia. Indications and contraindications are carefully evaluated.

A chapter is devoted to miscellaneous indications for spinal anesthesia, such as intestinal obstruction (diagnosis), temperature studies of the lower extremities, megacolon, etc. Spinal anesthesia, in various surgical specialties, is discussed.

A very extensive bibliography is given in addition to a very satisfactory subject index.

The book is extremely comprehensive in its scope and is a very valuable contribution to the literature on this subject. It should be of inestimable value to the anesthetist, the student and to individuals interested in the question of spinal anesthesia.

G. H. Y.

*The Primate Thalamus.* By A. EARL WALKER, M.D., Instructor in Neurosurgery, The University of Chicago. 321 pages; 15.5 × 23.5 cm. The University of Chicago Press, Chicago, Illinois. 1938. Price, \$3.00.

The present volume is an excellent discussion of the anatomy and physiology of the thalamus of the macaque. It begins with an historical introduction which, though

brief, brings the material well up to date. The second chapter describes Walker's method of study and experimental material including a brief review of the Nissl and Marchi technics. The author devotes the third chapter to a description of the gross and nuclear structure of the macaque thalamus. The remainder of the book, four substantial chapters, includes: (a) a description of the afferent connections of the thalamus; (b) a discussion of the relation of the thalamus to the cerebral cortex; (c) a rather short consideration of the relation of the geniculate bodies to the cerebral cortex; (d) an excellent summary of the anatomical, physiological and clinical significance of the thalamic region of the brain. When the author discusses the connections of the thalamus, he is at his best. He has consulted all of the literature dealing with each one of the known connections and has verified these connections in the macaque brain by means of ablation of parts of the brain and the study of degeneration of the connections. By these means he has been able to verify some opinions and to act as referee in cases where there is a disagreement. Unfortunately, as a general rule, he only cites one experimental case of his own to show the connections but it is to be presumed, since these experiments lasted over a period of six years, that each experiment has been verified by other similar operations. An attempt to discern the damage to the nuclei and their connections is the primary purpose of each of these experiments but there is a description of the behavior of the animal which is also of value in showing the physiological picture. The gross areas of the brain affected are shown by drawings of the whole brain as well as of sample serial sections showing the local damage. There is, of course, little discussion of the possible emotional function of the thalamus.

The book is a decided contribution to our knowledge of the anatomical connections and the physiological significance of this little-known part of the nervous system, as well it should be, since the work was done under the direction of Percival Bailey, John F. Fulton and Bernardus Brouwer.

L. S. S.

*Diabetes Insipidus.* By C. FISHER, W. R. INGRAM, and S. W. RANSON. 212 pages; 21 × 28 cm. Edwards Brothers, Inc., Ann Arbor, Michigan. 1938. Price, \$5.00.

The exact anatomical location of lesions which will cause diabetes insipidus has long been a controversial matter from both a clinical and experimental viewpoint. The excellent work of Fisher, Ingram, and Ranson definitely localizes such lesions to the supra-optic-hypophyseal system. The authors further demonstrate that the symptoms of permanent polyuria and polydipsia will not appear unless there is normal anterior pituitary tissue present. Their experimental work is valuable for its careful histological examinations, the production of localized lesions, and the large series of animals used (cats and monkeys).

In the latter part of the book the authors review the literature and try to fit the conflicting data of other investigators into their conception of diabetes insipidus. From an anatomical standpoint the picture appears to be consistent and logical but a clear-cut analysis of the subject is impossible until some of the physiological mechanisms involved are more completely understood. As Fisher, Ingram, and Ranson indicate in their introduction the reader whose time is limited will find the more important results of their investigation presented in Chapters III, V, X, and XI.

J. H.

*The Cerebrospinal Fluid and Its Relation to the Blood; A Physiological and Clinical Study.* By SOLOMON KATZENELBOGEN. xix plus 468 pages; 16 × 23.5 cm. The Johns Hopkins Press, Baltimore, Maryland. 1935. Price, \$5.00.

The purpose of this book has been to review and analyze the vast material which has accumulated on the cerebrospinal fluid and its relation to the blood. The author has added his own researches to the work of others in an attempt to formulate the actual state of our present knowledge. This purpose has been very well achieved.

The introductory chapters deal with the origin, mode of formation, and circulation of the cerebrospinal fluid. The existing theories are discussed pro and con, and one is impressed that much remains to be done before these fundamental problems are settled. The remaining chapters deal with the physico-chemical constitution of the cerebrospinal fluid in comparison with the blood in both physiological and pathological states. The hemato-encephalitic barrier is fully discussed, and individual chapters deal with the chief chemical constituents of the spinal fluid. The only important omission is the lack of adequate discussion of the total protein content of spinal fluid.

A short chapter is devoted to the important relation of pressure in blood and cerebrospinal fluid. The function of barrier between cerebrospinal fluid and blood is ably discussed, and methods of study of this function are reviewed. The clinical application of artificial alteration of barrier permeability is fully presented.

The book is not a concise guide for clinical study of the cerebrospinal fluid, but is rather a critical reference work on the state of our present knowledge of the cerebrospinal fluid. Both sides of controversial material are presented. The organization of the work is good, each chapter contains a brief summary, and a valuable bibliography is appended. The index is well prepared. The author has made a very valuable contribution and his book is recommended as an excellent reference work.

J. G. A., JR.

*The Intellectual Functions of the Frontal Lobes; A Study Based upon Observation of a Man after Partial Bilateral Lobectomy.* By RICHARD M. BRICKNER. xvi plus 354 pages; 14.5 × 20 cm. The Macmillan Company, New York. 1936. Price, \$3.50.

This monograph is devoted to the study of a patient after partial bilateral frontal lobectomy. In 1930 Dandy removed 116 grams of brain tissue from both frontal lobes in the course of removing a parasagittal meningioma. One year following operation, the patient came under the author's care. During the second postoperative year he was studied carefully by means of formal psychological and neurological tests, as well as by informal continual observation in his daily life.

The literature contains many studies on patients with infections and injuries to the frontal lobe, but this is the first report of a carefully studied patient after partial double frontal lobectomy. The author has summarized his conclusions, and they represent an important contribution to the study of frontal lobe function. There are many factors, however, which enter into the interpretation of functional changes following ablation experiments, so that too much weight cannot be placed on the study of a single case, however carefully it may be done. Symptoms referable to destruction of brain tissue must be differentiated from the positive symptoms which arise as release phenomena from other parts of the intact brain, and herein lies the great difficulty in analyzing ablation experiments, both in animal experiments and in man.

The book contains a brief review of the existing literature on symptoms of frontal lobe injury, a careful presentation of the observations of the patient for more than a year, and several chapters dealing with the interpretation of this study. The monograph is an important contribution, and will be read with interest by the neurologist, psychiatrist, and psychologist.

J. G. A., JR.

# COLLEGE NEWS' NOTES

## NEW OFFICERS, REGENTS AND GOVERNORS

At the General Business Meeting of the American College of Physicians, held on March 30, 1939, in connection with the 23rd Annual Session of the College at New Orleans, Dr. O. H. Perry Pepper, Philadelphia, was inducted as President and the following elections took place:

President-Elect .....	James D. Bruce, Ann Arbor
1st Vice President .....	Allen A. Jones, Buffalo
2nd Vice President .....	Gerald B. Webb, Colorado Springs
3rd Vice President .....	J. Morrison Hutcheson, Richmond

For the term expiring 1942, the following were elected (\* reelected) to the Board of Regents:

Charles T. Stone, Galveston  
 Reginald Fitz, Boston  
 \*Egerton L. Crispin, Los Angeles  
 Francis G. Blake, New Haven  
 William J. Kerr, San Francisco

Dr. Kerr and Dr. Stone served during the past year as President and 3rd Vice President, respectively.

For the term expiring 1942, the following were elected to the Board of Governors:

Oliver C. Melson .....	ARKANSAS—Little Rock
Ernest H. Falconer .....	Northern CALIFORNIA—San Francisco
Fred M. Smith .....	IOWA—Iowa City
Joseph E. Knighton .....	LOUISIANA—Shreveport
Henry R. Carstens .....	MICHIGAN—Detroit
Edgar van Nuys Allen .....	MINNESOTA—Rochester
A. Comingo Griffith .....	MISSOURI—Kansas City
Robert B. Kerr .....	NEW HAMPSHIRE—Manchester
George H. Lathrope .....	NEW JERSEY—Newark
Charles H. Cocke .....	NORTH CAROLINA—Asheville
Julius O. Arnson .....	NORTH DAKOTA—Bismarck
Alexander M. Burgess .....	RHODE ISLAND—Providence
Kenneth M. Lynch .....	SOUTH CAROLINA—Charleston
Paul K. French .....	VERMONT—Burlington
Walter B. Martin .....	VIRGINIA—Norfolk
Charles E. Watts .....	WASHINGTON—Seattle
Walter E. Vest .....	WEST VIRGINIA—Huntington
Hughes A. Farris .....	MARITIME PROVINCES—St. John, Can.
Charles F. Moffatt .....	QUEBEC—Montreal, Can.

Dr. Charles H. Turkington, Litchfield, Conn., was elected for the term expiring 1941, succeeding Dr. Francis G. Blake who was elected to the Board of Regents.

Dr. Walter E. Vest, for a number of years Governor for West Virginia and re-elected at the New Orleans Session, has since resigned as Governor because of too great a multiplicity of other duties and responsibilities, and, in accordance with provisions of the Constitution and By-Laws, the President, Dr. O. H. Perry Pepper, has appointed Dr. Albert H. Hoge, of Bluefield, as Governor for West Virginia, to serve until the next regular election.

## CLEVELAND SELECTED FOR 1940 SESSION OF THE COLLEGE

At a meeting of the Board of Regents at New Orleans March 31, it was voted to hold the 1940 Session of the American College of Physicians in the City of Cleveland. Announcements will be made later of the appointment of a General Chairman, local committees, and of other details.

## ELECTIONS TO MEMBERSHIP

At the 1939 Convocation of the American College of Physicians at New Orleans, 228 physicians were inducted into Fellowship, representing 39 States, Puerto Rico, 4 Provinces of Canada, the Medical Corps of the U. S. Army, U. S. Navy and the U. S. Public Health Service. The list herewith follows:

William Bluford Adamson .....	Abilene, Tex.
William Wallace Alexander .....	Florence, Ala.
William Hackney Algie .....	Kansas City, Kan.
Ellery George Allen .....	Syracuse, N. Y.
Frederic A. Alling .....	Newark, N. J.
Ellsworth Lyman Amidon .....	Burlington, Vt.
George Edward Anderson .....	Brooklyn, N. Y.
James Brent Anderson .....	M. C., U. S. Army
Russell Sherwood Anderson .....	Erie, Pa.
Fred Ernest Angle .....	Kansas City, Kan.
Kenneth Ellmaker Appel .....	Philadelphia, Pa.
Arthur Graham Asher .....	Kansas City, Mo.
Dudley Curtis Ashton .....	Beckley, W. Va.
John Martin Askey .....	Los Angeles, Calif.
Benjamin May Baker, Jr. ....	Baltimore, Md.
Fred Eugene Ball, Jr. ....	Chicago, Ill.
Walter Merritt Bartlett .....	Benton Harbor, Mich.
Julian Cox Barton .....	San Antonio, Tex.
James Bernard Berardi .....	Dwight, Ill.
Frank Hartsuff Bethell .....	Ann Arbor, Mich.
Launcelot Minor Blackford .....	Atlanta, Ga.
Theodore Liston Bliss .....	Akron, Ohio
Ralph Bowen .....	Oklahoma City, Okla.
Ernest Lloyd Boylen .....	Portland, Ore.
Russell Stanton Bray .....	Providence, R. I.
Alexander Edward Brown .....	Rochester, Minn.
Charles Stanford Byron .....	Brooklyn, N. Y.
Walter Lawrence Cahall .....	Philadelphia, Pa.
Frank Benjamin Carr .....	Worcester, Mass.
Charles Evans Catchings .....	Woodville, Miss.
John Richard Cavanagh .....	Washington, D. C.
William Edward Chamberlain .....	Philadelphia, Pa.
Charles Belson Chapman .....	Welch, W. Va.
Anthony Caesar Cipollaro .....	New York, N. Y.
Thomas Sterling Claiborne .....	Atlanta, Ga.
Richard James Clark .....	Winchester, Mass.
Milton Bronner Cohen .....	Cleveland, Ohio
Everett Naughtin Collins .....	Cleveland, Ohio
William Johnston Cranston .....	Augusta, Ga.
Burrill B. Crohn .....	New York, N. Y.

Marion Tabb Davidson .....	Birmingham, Ala.
John Staige Davis, Jr. ....	New York, N. Y.
Elbert DeCoursey .....	M. C., U. S. Army
Morris Deitchman .....	Youngstown, Ohio
Samuel Dessoiff .....	Washington, D. C.
Bruce Hutchinson Douglas .....	Detroit, Mich.
Ardrey Whidden Downs .....	Edmonton, Alta., Canada
Paul A. Draper .....	Colorado Springs, Colo.
Earl Danford DuBois .....	Portland, Ore.
Garfield George Duncan .....	Philadelphia, Pa.
Harry Anthony Durkin .....	Peoria, Ill.
Herbert Robert Edwards .....	New York, N. Y.
Arthur Carlton Ernstene .....	Cleveland, Ohio
Earl Bradley Erskine .....	Jamaica, L. I., N. Y.
Stanley Erwin .....	Jacksonville, Fla.
Vernon Lawrence Evans .....	Aurora, Ill.
Harold Korb Eynon .....	Collingswood, N. J.
Marcos Fernan-Nunez .....	Milwaukee, Wis.
Maxwell Finland .....	Boston, Mass.
George Fordham .....	Powellton, W. Va.
James Hedges Forsee .....	M. C., U. S. Army
Daniel Parsons Foster .....	Detroit, Mich.
Stuart Oliver Foster .....	Washington, D. C.
George Charles Henry Franklin .....	M. C., U. S. Army
Leslie Howson French .....	Washington, D. C.
Max L. Garon .....	Louisville, Ky.
Warren Monroe Gilbert .....	Rome, Ga.
Edgar Gilmore Givhan, Jr. ....	Birmingham, Ala.
Stanley Milton Goldhamer .....	Ann Arbor, Mich.
Rufus Quitman Goodwin .....	Oklahoma City, Okla.
Roderick John Gordon .....	London, Ont., Canada
James John Gorman .....	El Paso, Tex.
Raymond Leslie Gregory .....	Washington, D. C.
William Hugh Griffith .....	Huron, S. D.
John Carl Grill .....	Milwaukee, Wis.
Ernest Elvin Hadley .....	Washington, D. C.
James Addison Halsted .....	Dedham, Mass.
Jesse Dewey Hamer .....	Phoenix, Ariz.
Leland Potts Hawkins .....	Los Angeles, Calif.
John N. Hayes .....	Saranac Lake, N. Y.
John Herbert Leyda Heintzelman .....	Pittsburgh, Pa.
Louis Max Hickernell .....	Syracuse, N. Y.
Charles Spencer Higley .....	Cleveland, Ohio
John Palmer Hilton .....	Denver, Colo.
Blair Holcomb .....	Portland, Ore.
Frederick Redding Hood .....	Oklahoma City, Okla.
Frank Stephen Horvath .....	Washington, D. C.
Joseph Warren Hundley, Jr. ....	Philadelphia, Pa.
Raymond Hussey .....	Baltimore, Md.
Charles Louis Ianne .....	San Jose, Calif.
Mendel Jacobi .....	Brooklyn, N. Y.
Roy R. Jamieson .....	Chicago, Ill.



Hartwell Joiner .....	Gainesville, Ga.
Oswald Roberts Jones .....	New York, N. Y.
John Leonard Kantor .....	New York, N. Y.
Egon Emil Kattwinkel .....	Auburndale, Mass.
Harold R. Keeler .....	Philadelphia, Pa.
Wilbur Floyd Keller .....	Oklahoma City, Okla.
Edwin John Kepler .....	Rochester, Minn.
Stockton Kimball .....	Buffalo, N. Y.
Edward Sandling King .....	Wake Forest, N. C.
Theodore G. Klumpp .....	Washington, D. C.
Enrique Koppisch .....	San Juan, P. R.
Albert Franklin Kuhl .....	Dayton, Ohio
Louis Harold Landay .....	Pittsburgh, Pa.
Isidore Lattman .....	Washington, D. C.
Fay Atkinson LeFevre .....	Cleveland, Ohio
Noble Day Leonard .....	North Chicago, Ill.
Aleksei A. Leonidoff .....	Poughkeepsie, N. Y.
Robert Milton Lintz .....	New York, N. Y.
Louis Maxwell Lockie .....	Buffalo, N. Y.
Harold Charles Lueth .....	Evanston, Ill.
Jeremiah Fletcher Lutz .....	York, Pa.
Merl Lonner Margason .....	Portland, Ore.
Arthur Ashley Marlow .....	La Jolla, Calif.
Paul Bernard Mason .....	Sheboygan, Wis.
Lorenzo Dow Massey .....	Osceola, Ark.
Joseph Daniel McCarthy .....	Omaha, Nebr.
Clarke M. McColl .....	Detroit, Mich.
Robert Hall McConnell .....	New York, N. Y.
Ernest Perry McCullagh .....	Cleveland, Ohio
Robert Hugh McDonald .....	Cleveland, Ohio
Thomas Hodge McGavack .....	New York, N. Y.
Bernard Edward McGovern .....	San Fernando, Calif.
Ross T. McIntire .....	M. C., U. S. Navy
John Wendell McKenzie .....	Charlottetown, P. E. I., Canada
John McDowell McKinney .....	New York, N. Y.
James Bowron McLester .....	Birmingham, Ala.
Hector James McNeile .....	New York, N. Y.
Edgar Marion McPeak .....	San Antonio, Tex.
Perry Julius Melnick .....	Chicago, Ill.
Harold Russell Merwarth .....	Brooklyn, N. Y.
Solomon George Meyers .....	Detroit, Mich.
William Grady Mitchell .....	San Angelo, Tex.
Herman John Moersch .....	Rochester, Minn.
Merle Wayland Moore .....	Portland, Ore.
Carlyle Morris .....	Metuchen, N. J.
Carlisle Morse .....	Louisville, Ky.
Charles Scott Mudgett .....	M. C., U. S. Army
Bert Ernest Mulvey .....	Oklahoma City, Okla.
Harold A. Murray .....	Newark, N. J.
Elmer Ray Musick .....	Oklahoma City, Okla.
John Ernest Nelson .....	Seattle, Wash.
Charles Fay Nichols .....	Philadelphia, Pa.

Howard Miller Odel .....	Rochester, Minn.
Forrest Ralph Ostrander .....	M. C., U. S. Army
Wendell Heath Paige .....	Brownwood, Tex.
Harold Dwight Palmer .....	Rockford, Ill.
Paul H. Parker .....	Jenkintown, Pa.
Emmet Forrest Pearson .....	Springfield, Ill.
Louis Leo Perkel .....	Jersey City, N. J.
Richard Oscar Pfaff .....	Des Moines, Iowa
Theodore John Pfeffer .....	Racine, Wis.
Charles Aden Poindexter .....	New York, N. Y.
Ralph Emmett Porter .....	U. S. Public Health Service
William Henry Potts, Jr. ....	Dallas, Tex.
Milton James Quinn .....	Winchester, Mass.
William Orville Ramey .....	Cincinnati, Ohio
Edward Randall, Jr. ....	Galveston, Tex.
Stanley Philip Reimann .....	Philadelphia, Pa.
Anthony Joseph Rejent .....	Toledo, Ohio
Clarence E. Reyner .....	Detroit, Mich.
Henry Barber Richardson .....	New York, N. Y.
Hugo Roesler .....	Philadelphia, Pa.
Saul Rosenzweig .....	Detroit, Mich.
William Ward Rucks, Jr. ....	Oklahoma City, Okla.
Zachary Sagal .....	New York, N. Y.
Raymond Arthur Sands .....	Santa Monica, Calif.
David Jacob Sandweiss .....	Detroit, Mich.
Howard Russell Sauder .....	Wheeling, W. Va.
Theresa Scanlan .....	New York, N. Y.
Philipp J. R. Schmahl .....	New York, N. Y.
Henry Lenzen Schmitz .....	Chicago, Ill.
Robert Jacob Schneck .....	Detroit, Mich.
Seymour Crandall Schwartz .....	M. C., U. S. Army
Walter de Mouilpied Sriver .....	Montreal, Que., Canada
William Corr Service .....	Colorado Springs, Colo.
Samuel Charlton Shepard .....	Tulsa, Okla.
Charles Shookoff .....	Brooklyn, N. Y.
Stanley D. Simon .....	Cincinnati, Ohio
Edwin J. Simons .....	Swanville, Minn.
Carter Smith .....	Atlanta, Ga.
Richard Mays Smith .....	Dallas, Tex.
Leon Judah Solway .....	Toronto, Ont., Canada
Louis Sommer .....	Cincinnati, Ohio
Hyman I. Spector .....	St. Louis, Mo.
Frederick George Speidel .....	Louisville, Ky.
Harold Edmond Speight .....	Middletown, Conn.
William Arnold Stafne .....	Moorhead, Minn.
Dean Field Stanley .....	Decatur, Ill.
Robert Morgan Stecher .....	Cleveland, Ohio
Walter Ralph Steiner .....	Hartford, Conn.
Bernard Sternberg .....	Brooklyn, N. Y.
Harold Wentworth Stevens .....	Duxbury, Mass.
Colin Campbell Stewart .....	Hanover, N. H.
Harold Julian Stewart .....	New York, N. Y.
Robert Thomas Sutherland .....	Oakland, Calif.

Earl Richard Templeton .....	Washington, D. C.
Charles Roberts Thomas .....	Chattanooga, Tenn.
Daniel Rees Thomas .....	Knoxville, Tenn.
Cornelius Horace Traeger .....	New York, N. Y.
John William Trask .....	Chelsea, Mass.
John Poag Tucker .....	Cleveland, Ohio
Herbert John Ulrich .....	Buffalo, N. Y.
Harry Eduarde Ungerleider .....	New York, N. Y.
Louis Ashley Van Kleeck .....	Manhasset, N. Y.
Joe Edmund Walker .....	Long Beach, Calif.
Fonso Butler Watkins .....	Morganton, N. C.
Ralph Martin Watkins .....	Cleveland, Ohio
Robert Briggs Watson .....	Wilson Dam, Ala.
Morris M. Weiss .....	Louisville, Ky.
John Murray Welch .....	M. C., U. S. Army
George Louis Weller, Jr. ....	Washington, D. C.
Jacob Werne .....	Jamaica, L. I., N. Y.
Henry L. C. Weyler .....	Providence, R. I.
Joseph Francis Whinery .....	Newark, N. J.
Joseph Hall Whiteley .....	M. C., U. S. Army
Jerome Andrew Whitney .....	Longmeadow, Mass.
James Newton Williams .....	Richmond, Va.
Julius Lane Wilson .....	New Orleans, La.
Frank McLeod Wiseley .....	Findlay, Ohio
Mast Wolfson .....	Monterey, Calif.
Charles Hamilton Wolohon .....	Takoma Park, Washington, D. C.
John Olen Woods .....	New Castle, Pa.
S. Bernard Wortis .....	New York, N. Y.
Arthur Thomas Wyatt .....	Lillington, N. C.
Dwight Moody Young .....	M. C., U. S. Army
Francis Eugene Zemp .....	Columbia, S. C.

At a meeting of the Board of Regents on March 26, the following were elected to Associateship, making a total of 204 new Associates since the preceding Annual Session:

William Arnold Douglas Anderson .....	Memphis, Tenn.
Arthur Carl Bachus .....	Powers, Mich.
Walter Hilmar Baer .....	Peoria, Ill.
Gordon Wesley Balyeat .....	Ann Arbor, Mich.
Andrew L. Banyai .....	Wauwatosa, Wis.
William H. Barker .....	Baltimore, Md.
Maurice C. Barnes .....	Waco, Tex.
Clifford Albert Best .....	M. C., U. S. Army
Henry Grady Bevil .....	Beaumont, Tex.
Edward Bigg .....	Ann Arbor, Mich.
Samuel Blinder .....	New York, N. Y.
Rankin Clay Blount .....	Lexington, Ky.
Joseph Emile Blum, Jr. ....	New Orleans, La.
Charles Andrew Bohnengel .....	New York, N. Y.
Edmund Clyde Boots .....	Pittsburgh, Pa.

DeVere Robert Boyd .....	Muskegon, Mich.
George Nelson Burger .....	Athens, Ohio
George Warren Burnett .....	Oil City, Pa.
Joseph Bishop Cady .....	Rochester, Minn.
Franklin Chester Cassidy .....	Livermore, Calif.
Edwin Gurney Clark .....	Nashville, Tenn.
James W. Colella .....	Binghamton, N. Y.
Jay Cecil Crager .....	Beaumont, Tex.
Lloyd Lorenzo Cullimore .....	Provo, Utah
Haydn Harrison Cutler .....	Rochester, Minn.
Joseph Steven D'Antoni .....	New Orleans, La.
Boni James De Laureal .....	New Orleans, La.
Nelson Wright Diebel .....	Detroit, Mich.
Ray S. Dixon .....	Detroit, Mich.
Ralph Lafayette Drake .....	Wichita, Kan.
Paul Strimple Fancher .....	M. C., U. S. Army
Robert Hanna Felix .....	Lexington, Ky.
David Ferguson, Jr. ....	Washington, D. C.
Hugh Francis Folsom .....	Southborough, Mass.
Hugh Frederick Freidell .....	Santa Barbara, Calif.
Chester Sebastian Fresh .....	New Orleans, La.
Linus Jos. Foster .....	Detroit, Mich.
Silas Crume Fulmer .....	Little Rock, Ark.
Lawrence Bernard Gang .....	Huntington, W. Va.
Jay McKinley Garner .....	Winnetka, Ill.
Thomas Cresson Garrett .....	Philadelphia, Pa.
Frederick A. J. Geier .....	Washington, D. C.
Olin Burr Gober .....	Temple, Tex.
Frederick Goldman .....	Galveston, Tex.
Kenneth George Gould .....	M. C., U. S. Army
John Quentin Griffith .....	Philadelphia, Pa.
Randolph Bryan Griiman, Jr. ....	Norfolk, Va.
Edward Bertram Grossman .....	New York, N. Y.
James Roby Gudger .....	New York, N. Y.
James Lonnie Hamilton .....	Chattanooga, Tenn.
Paul Victor Hamilton .....	Cincinnati, Ohio
Maurice Hardgrove .....	Milwaukee, Wis.
Leon Hughes Hetherington .....	Pittsburgh, Pa.
Clifton Keck Himmelsbach .....	Lexington, Ky.
Milford Leroy Hobbs .....	Burlington, Vt.
Emory Dallas Hollar .....	Vernon, Tex.
J. Sudler Hood .....	Clearwater, Fla.
William James Hutchinson .....	Galveston, Tex.
William Reginald Jackson .....	Kansas City, Mo.
Joseph Francis Jenovese .....	Rochester, Minn.
Carl Edward Johnson .....	Morgantown, W. Va.
Edward Morgan Jones .....	Endicott, N. Y.
Robert Harold Jones .....	Montgomery, W. Va.
Aaron Arnold Karan .....	Liberty, N. Y.
Franklin Hartman Kilgore .....	Houston, Tex.
Otis Gardner King .....	Bluefield, W. Va.

Alfred Edward Koehler .....	Santa Barbara, Calif.
Charles John Koerth .....	San Antonio, Tex.
Joseph Rudolph Kriz .....	New Orleans, La.
Joseph Durel Landry .....	New Orleans, La.
Charles Wesley Layne .....	Newburgh, N. Y.
Albert Theodore Leatherbarrow .....	Hampton Station, N. B., Can.
Seaborn Joseph Lewis .....	Beaumont, Tex.
Julian Sax Long .....	Wilkes-Barre, Pa.
Philip Lukens .....	Ambler, Pa.
Tim Joseph Manson .....	Chattanooga, Tenn.
Frederick Eugene Marsh .....	Chattanooga, Tenn.
Floyd Thomas McIntire .....	San Angelo, Tex.
Delbert H. McNamara .....	Santa Barbara, Calif.
James Douglas Lannance McPheeters .....	Chattanooga, Tenn.
John Patrick McVay .....	Seattle, Wash.
Francis Ralph Meyers .....	Paterson, N. J.
R. Bretney Miller .....	Boston, Mass.
Samuel Mirsky .....	Ottawa, Ont., Can.
Lester M. Morrison .....	Philadelphia, Pa.
Emma Sadler Moss .....	New Orleans, La.
Walter Scott Neff .....	Virginia, Minn.
Virgil Frank Neumann .....	Norwich, Conn.
Thomas Ochsner Nuzum .....	Janesville, Wis.
Arthur Burke O'Brien .....	Rochester, N. Y.
Louis Bonner Owens .....	Cincinnati, Ohio
Robert Clinton Page .....	Mount Vernon, N. Y.
Sol Parent .....	Newark, N. J.
Aaron Robert Peskin .....	New York, N. Y.
Helen Sinclair Pittman .....	Boston, Mass.
Francis Marion Pottenger, Jr. ....	Monrovia, Calif.
Harry William Primakoff .....	Baltimore, Md.
Harry Malcolm Read .....	York, Pa.
Edward Conrad Reifenstein, Jr. ....	Syracuse, N. Y.
Murray Lambert Rich .....	Covington, Ky.
Archie Marvin Roberts .....	Los Angeles, Calif.
Frank Hurd Robinson, Jr. ....	New York, N. Y.
John Roy Rodger .....	Bellaire, Mich.
Abraham Rudy .....	Boston, Mass.
Nelson Gorham Russell, Jr. ....	Buffalo, N. Y.
Otis B. Schreuder .....	M. C., U. S. Army
Grady Oscar Segrest .....	Mobile, Ala.
Joseph Haskell Shaffer .....	Detroit, Mich.
William W. Shapiro .....	Chicago, Ill.
John Charles Sharpe .....	Omaha, Nebr.
Walter Charles Smallwood .....	Long Beach, Calif.
Opie Norris Smith .....	Greensboro, N. C.
Martin Jos. Sokoloff .....	Philadelphia, Pa.
Harold Jones Starr .....	Chattanooga, Tenn.
Alfred Stengel, Jr. ....	Philadelphia, Pa.
Ralph Eugene Swope .....	New York, N. Y.
Richard Carmichael Tilghman .....	Baltimore, Md.

Harry Burger Thomas .....	York, Pa.
Harry Edward Thompson .....	Tucson, Ariz.
Lucius Newton Todd .....	Augusta, Ga.
Arthur Raymond Twiss .....	Ann Arbor, Mich.
Hiram Eugene Upton .....	Burlington, Vt.
Don Conklin Wakeman .....	Topeka, Kan.
Frank Bolles Wakeman .....	M. C., U. S. Army
Walter Weissenborn .....	Hartford, Conn.
John Francis Whalen .....	Altadena, Calif.
Merritt Bryant Whitten .....	Dallas, Tex.
Walter John Wilson, Jr. ....	Detroit, Mich.
Francis Roman Wise .....	York, Pa.
Sidney Elmer Wolpaw .....	Cleveland, Ohio
Charles Tindal Young .....	M. C., U. S. Army

#### NEW LIFE MEMBERS

The following Fellows have become Life Members of the American College of Physicians on March 9 and March 15, respectively:

Dr. Frank Bethel Cross, Brooklyn, N. Y.  
 Dr. James Alexander Lyon, Washington, D. C.

#### GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following gifts to the College Library of publications by members:

#### *Reprints*

Dr. Archie H. Beard, F.A.C.P., Minneapolis, Minn.—5 reprints;  
 Dr. Warren Coleman, F.A.C.P., Augusta, Ga.—2 reprints;  
 Dr. Frank J. Holroyd (Associate), Princeton, W. Va.—1 reprint;  
 Dr. Louis I. Kramer, F.A.C.P., Providence, R. I.—2 reprints;  
 Dr. Fay A. LeFevre, F.A.C.P., Cleveland, Ohio—2 reprints;  
 Dr. Oliver T. Osborne, F.A.C.P., New Haven, Conn.—1 reprint;  
 Dr. Samuel S. Paley (Associate) New York, N. Y.—1 reprint;  
 Dr. Kenneth Phillips, F.A.C.P., Miami, Fla.—2 reprints;  
 Dr. Jacob Schwartz (Associate), Brooklyn, N. Y.—1 reprint;  
 Dr. Albert Soiland, F.A.C.P., Los Angeles, Calif.—5 reprints;  
 Dr. Peter J. Steincrohn (Associate), Hartford, Conn.—1 reprint.

#### VIRGINIA SECTIONAL MEETING

Fellows and Associates of the American College of Physicians from the State of Virginia held a meeting during March in Norfolk, with forty members present. The Virginia group is now holding three meetings a year, and each one is becoming more attractive and of more benefit. One is a social meeting and the other two are strictly scientific. The meetings are held in different parts of the State. Dr. T. Dewey Davis, F.A.C.P., of Richmond is chairman of the Virginia section, and Dr. Charles M. Caravati, F.A.C.P., of Richmond is the secretary. The group and the officers function under Dr. J. Morrison Hutcheson, F.A.C.P., who has been the Governor for the State of Virginia for several years.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., addressed a joint meeting of the Section on Research, Academy of Stomatology, Section on Research, Philadelphia County Dental Society and Section on Stomatology, Philadelphia County Medical Society, on Friday, February 24, 1939, on "The Rôle of Deficiency Disease in Dentistry, with Special Reference to Vitamins and Minerals."

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Dr. Isidore W. Held, F.A.C.P., Clinical Professor of Medicine at New York University College of Medicine, addressed the 93rd annual banquet of the Northern Medical Association of Philadelphia, March 20, on "Jefferson, My Alma Mater; and Philadelphia as a Medical Center." Dr. David Riesman, F.A.C.P., Philadelphia, acted as toastmaster, and Dr. E. J. G. Beardsley, F.A.C.P., Clinical Professor of Medicine at Jefferson Medical College, was another of the speakers.

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Dr. Hubert C. King, F.A.C.P., President of the Academy of Medicine of Cleveland delivered an address on "The Physician," in connection with a forum discussion on the social and economic aspects of medicine, sponsored by Western Reserve University School of Medicine from March 17 to May 9. Dr. King's address was delivered on March 31, and dealt with the recent trends in premedical and medical education, certification in specialties, the distribution of physicians in the United States, physicians' incomes as revealed in special surveys, etc. His paper was intended to reveal the rôle of the physician in connection with the forum on "The Physician and Dentist."

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Dr. J. C. Doane, Professor of Clinical Medicine of Temple University Medical School of Philadelphia addressed the York County Medical Society at York, Pa., on Saturday, March 18, 1939. The subject was "Alcoholism, Its Diagnosis and Treatment"; also the Chester County Medical Society at West Chester, Pa., on Tuesday, March 21, 1939. The subject was "Clinical Interpretation of the Symptoms Pain."

## RECENT ANNOUNCEMENTS

## AMERICAN BOARD OF INTERNAL MEDICINE, INC.

Written examinations for certification by the American Board of Internal Medicine will be held in various sections of the United States on the third Monday in October and the third Monday in February.

Formal application must be received by the Secretary before August 20, 1939 for the October 16, 1939 examination, and on or before January 1 for the February 19, 1940 examination.

Application forms may be obtained from Dr. William S. Middleton, Secretary-Treasurer, 1301 University Avenue, Madison, Wisconsin, U. S. A.

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The Fourteenth Scientific Sessions of the American Heart Association will be held at the Hotel Jefferson, St. Louis, Missouri. The general cardiac program will be given on Friday, May 12, and the program of the Section for the Study of the Peripheral Circulation on Saturday, May 13.

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The 24th Annual meeting of the American Association of Industrial Physicians and Surgeons with the American Conference on Occupational Diseases and Industrial Hygiene will be held at the Hotel Statler, Cleveland, Ohio, June 5, 6, 7, and 8, 1939. A program of timely interest and importance will be presented by speakers of outstanding experience in all of the medical and engineering problems involved in industrial health. A cordial invitation is extended to all whose interests bring them in contact with these problems. Information regarding hotel accommodations, etc., may be obtained from A. G. PARK, Convention Manager, 540 North Michigan Avenue, Chicago.

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The American Physicians' Art Association, composed of members in the United States, Canada, and Hawaii, will hold its second Art Exhibit in the City Art Museum of St. Louis, May 14-20, 1939, during the annual session of the American Medical Association. Art pieces will be accepted for this art show in the following classifications: (1) oils both (a) portrait and (b) landscape; (2) water colors; (3) sculpture; (4) photographic art; (5) etchings; (6) ceramics; (7) pastels; (8) charcoal drawings; (9) book-binding; (10) wood carving; (11) metal work (jewelry). Practically all pieces sent in will be accepted. There will be over 60 valuable prize awards. For details of membership in this Association and rules of the Exhibit, kindly write to Max Thorek, M.D., Secretary, 850 Irving Park Blvd., Chicago, Ill., or F. H. Redewill, M.D., President, 521-536 Flood Bldg., San Francisco, Calif.

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The 63d annual convention of the American Association on Mental Defect will be held at the Palmer House in Chicago, Illinois, from May 3d to 6th, inclusive.

THE BALKAN MEDICAL UNION, in session at Istanbul, for the 5th Medical Week, *having taken into consideration* the terrible sufferings which a total war will bring upon the civil population of open towns together with the total lack of any adequate means of protection,

*and having discovered* that even in its restricted form the project of "sanitary towns" has not yet been adopted, and that all efforts made to protect civilians against chemical warfare have until now remained as proposals only, and that even the protocol prohibiting the use of asphyxiating gas has not yet been ratified by all nations,



*has therefore decided* to address itself to doctors of every nation with an appeal to take active measures and to fulfill this professional and humanitarian duty of awakening and stirring public opinion.

*The Balkan Medical Union believes* that only enlightened international opinion can make plain the imminence of the danger and the proved uselessness, even for the victor, of these terrible atrocities, and can thus lead to effective action.

The immutable truth that

*hate breeds only hate, and atrocity breeds vengeance* must be impressed on everyone.

PROF. DR. BENSIS, DR. SCARAMANGA (Athènes), DR. ZIKA MARKOVIĆ, PROF. DR. K. SAHOVIĆ, DR. M. SIMOVIĆ (Beograd), PROF. DR. GHEORGHIU, DR. POPESCU BUZEU (Bucarest), PROF. DR. ÂKIL MUHTAR ÖZDEN, PROF. SEDAT TAVAT, PROF. DR. A. SÜNEYL UNVER (İstanbul).

## OBITUARIES

### DR. DONALD GREGG

Dr. Donald Gregg (Fellow and Life Member), of Wellesley, died January 6, 1939 at Phillips House, Massachusetts General Hospital. He was in his sixtieth year.

Born in Hartford, Connecticut, he moved as a child to Colorado Springs, Colorado, attending the public schools there. He prepared for college at Cutler Academy, graduated from Harvard College in 1902 and received his degree from Harvard Medical School in 1907. He served his internship during 1908-1909 at the Massachusetts General Hospital, after which he served four years as resident physician of the Philippine General Hospital at Manila, Philippine Islands. During one year there he was assistant professor of tropical medicine at the University of the Philippines.

Dr. Gregg returned to the United States in 1912 and began practicing in Wellesley. He became associated with Dr. Channing in the direction of the Channing Sanitarium at Wellesley, taking full charge at the time of Dr. Channing's death in 1922.

Among his affiliations were memberships in the American Medical Association, Massachusetts Medical Society, American College of Physicians, American Neurological Association, American Psychiatric Association, New England Society of Psychiatry, Association for Research in Nervous and Mental Disease and American Psychopathological Association.

His widow, three brothers and three sisters survive him.

WILLIAM B. BREED, M.D., F.A.C.P.,  
Governor for Massachusetts.

### DR. JAMES WALLACE ESLER

James Wallace Esler, of 2737 Devonshire Place, N.W., Washington, D. C., died December 15, 1938, of sarcoma of the intestines. He was only forty-four years old and had been elected to Associateship in the American College of Physicians two years before his death. A prominent cardiologist in the national capital, he had a promising career tragically shortened. Very well liked by everyone, he has already been greatly missed.

Dr. Esler was born in Tarentum, Pa., October 27, 1894. He received an A.B. degree in 1916 from Washington and Jefferson College, and in 1920, an M.D. degree from the University of Pennsylvania School of Medicine. He spent the next year as an Instructor in Physiology and as a postgraduate research worker in physiology at his medical Alma Mater. After interning in the Pennsylvania Hospital, Philadelphia, from 1921 to 1923, he served for one year as chief resident at St. Christopher's Hospital, Philadelphia. From 1927 to 1928 he did postgraduate study in cardiology at the Massachusetts General Hospital, Boston.

From the time he began the practice of cardiology in the District of Columbia in 1928 he held the Professorship of Clinical Cardiology at the Georgetown University School of Medicine and served as an Associate in Medicine and Chief of the Cardiac clinics at Georgetown University Hospital. He also became associated later with the Central Dispensary and Emergency Hospital, and Garfield Memorial Hospital. Dr. Esler was a member of the American Medical Association, the Medical Society of the District of Columbia, and the Washington Heart Association, of which he was secretary for years and later president. He was a former member of the Allegheny County Medical Society (Pittsburgh).

Surviving are his widow, Mrs. Lillian Esler, a son, James Wallace Esler, Jr., and a brother, Russel J. Esler.

WALLACE M. YATER, M.D., F.A.C.P.,  
Governor for the District of Columbia.

### DR. LESSER KAUFFMAN

Dr. Lesser Kauffman, a Fellow of the American College of Physicians since 1916, died in Buffalo, New York, March 11, 1939, from a "heart attack."

Dr. Kauffman was born in Germany April 8, 1876, came to America when he was quite young and settled in Rochester, New York. He completed his undergraduate studies at the University of Rochester and was graduated from the University of Buffalo in 1904. He soon became associated with Dr. James W. Putnam, then Professor of Neurology at the University of Buffalo. Dr. Kauffman continued the practice of neurology and psychiatry throughout his medical career.

Dr. Kauffman was very active in the General Alumni Association of the University of Buffalo, and was first President of that group. His principal outside interest was music. He was most active in the Symphony Society and his work in bringing to Buffalo music of the highest type contributed to the greater appreciation of music in the city and the support of fine music throughout the country. He was also active in the Museum of Science and the Buffalo Historical Society.

Dr. Kauffman's activities in his profession and as a citizen were of the highest type.

Dr. Kauffman was unmarried and is survived by a sister in Pittsburgh and a brother in Rochester.

NELSON G. RUSSELL, M.D., F.A.C.P.,  
Governor for Western New York.

# ANNALS OF INTERNAL MEDICINE

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MAY, 1939

NUMBER 11

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## IN THE SPIRIT OF SERVICE\*

By WM. J. KERR, F.A.C.P., President of the American College of Physicians, *San Francisco, California*

"Where there is love of the art there also the love of man is"—Hippocrates

As members of the medical profession, we are becoming increasingly conscious that all is not well in our house. Doubts are being implanted in the minds of laymen concerning the efficacy of established practices which organized medicine has set up for the protection of society. Propaganda for the socialization of medical services is encountered on every hand. The motives for professional objection to even the most fantastic schemes for providing medical care are misunderstood.

There has never been a time when the medical profession has had so much to offer the people as in this year 1939. From research laboratories and the bedside, discoveries of great significance flow in increasing volume. In the fields of biophysics, physiology, biochemistry, chemotherapy, immunology, nutrition, endocrinology and in their spheres of clinical application, we witness the most remarkable scientific advances the world has ever known.

This is the Golden Age of medicine. We grow so accustomed to spectacular pronouncements that our critical faculties have been weakened. The reactions in the laboratories scarcely cease before the products of research are rushed to the bedside. It is said that the proprietary manufacturers, like prowling jackals awaiting the feast, embrace every opportunity to capitalize upon the discoveries. Witness the deluge of vitamin and endocrine products, the host of chemical compounds under many proprietary names, and the other nostrums distributed through the profession or sold directly to the public. These proprietary drugs are sold over the counter in variety drug stores where the dispensing department is well disguised behind an

\* Presented at the New Orleans meeting of the American College of Physicians, March 29, 1939.

It should be understood that any statements or comments made in this address or any opinions given are entirely personal and do not necessarily reflect the consensus of opinion of the membership of the American College of Physicians. It is not implied that the College has taken any action or intends to take any official action for the solution of any of the problems discussed.

array of cosmetics, liquors and lunch counters. Our large department stores are catering to the demand for vitamin products at an annual cost to the feminine consumer which would give her full medical protection. Authority should be granted to proper agencies charged with the enforcement of the Food and Drug Act to restrict high-pressure salesmanship dangerous to the welfare and safety of the public. The investigations of the Council of Pharmacy and Chemistry of the American Medical Association should be given wider publicity.

New methods for diagnosis and treatment should be carefully tested before being given to an expectant profession and through it to the trusting public. Too often the harmful effects of a new procedure or a new drug are not easily discernible. The producer (the research worker) has a great responsibility. There is no way for the distributor (the doctor) to judge the worth of new methods except by trial and error. In the end it is the consumer (the patient) who pays the bill and runs the risk, and he is usually in no position to know he has been injured or defrauded.

There has never been a time when the public has been so conscious of the current advances in science. People read of the modern miracles of medicine and are prepared to expect any pronouncement in its name. Since they are unable to discriminate, pseudo-science and cultism flourish to an unparalleled degree in this most enlightened scientific age.

The public are interested in better medical care. We are faced with an increasing demand for a more equable distribution of medical services. Our country has been almost the last to meet this issue. It must be faced wisely for the benefit of all the people and *in such ways that the quality of services shall not be impaired*. It should be apparent to anyone who attended the Washington Health Conference last July that over half the people of our country are demanding the benefits that they believe could be obtained by a more even distribution of these services. Organized medicine has been outspoken in its opposition to some of the proposals advanced for a reorganization of medical practice, because its leaders believe that these proposals if adopted will result in inferior rather than improved service. Other professional groups contributing to the care of the sick apparently agree that some changes are urgently needed, and many reputable members of the medical profession sincerely believe that the proposals made in Washington offer a basis for solution. There has been much criticism of the methods used in the preliminary survey of existing conditions, but no more surveys are needed to show that the low-income groups have more sickness and higher death-rates than those in the higher income group. In recent months many of the objections raised by organized medicine have been withdrawn, leaving only the subject of compulsory health insurance for further study and discussion. Anyone who heard the recent demands in Washington must be impressed by the sincerity of the appeal for better health. Never has there been so great and important an appeal to the professional groups contributing to the care of the sick. There are some who hold that the

appeal on the part of some of the groups was ingenuous. Among the representatives of workers with low incomes were some who held the extreme view that all services to the sick should be free and based upon general taxation. It was evident, however, that most of the groups represented expected to contribute toward the cost of services according to their ability to pay, with such assistance by employers and by the public through taxation as would be required to insure the highest quality of medical service.

It is the prevailing opinion that only the rich and the poor secure the best or even satisfactory medical care and that the groups of people with moderate or low incomes are unable to secure proper treatment. This is true within certain limits. The very poor are able to secure excellent care in centers where well established endowed or tax-supported hospitals and ambulatory clinics are provided. Most or all of the cost of services to these people is borne now by the public in one way or another. In private practice this group is cared for by physicians without thought of compensation. The personal services are rendered in a spirit of charity. It is obvious that practitioners cannot afford to pay for the necessary expensive diagnostic and therapeutic services which may be required. Doctors ~~take~~ great pride in their charitable acts, but when a large proportion of their time and substance is donated, the economic burden is greater than they can bear. In those places where free clinics and free hospital facilities are not available, complete medical care cannot be provided. The doctor cannot carry the entire load and survive. The contributions made by the medical profession in these years of depression are enormous and have been estimated by our distinguished president of the American Medical Association, Dr. Irvin Abell, at a million dollars a day. This is probably a conservative estimate. Doctors, led by charitable motives, are being subjected to an economic pressure which is bringing the income of many of them below the level of respectability and often below the level of mere subsistence. Among those contributing to the care of the needy sick, they alone are giving freely of their services while all others are paid.

How does it fare with the large middle group? People with low or moderate incomes are unable to pay for full medical services. They seldom see a doctor unless symptoms are severe, and often it is too late to secure the best result. They receive little or no preventive treatment. They can neither save for catastrophic illness nor contribute to a fund for proper distribution of medical services.

It is generally stated that the well-to-do have the best of care. The rapidly vanishing group of the wealthy members of society can afford to secure the best medical services. However, it does not follow that they get it. The chief obstacle lies in the tendency to over-specialization in our larger centers. Many well-to-do families have no one general physician who acts as the family advisor and who arranges for the services of specialists when needed. They often go directly to specialists; each member of the family makes his or her own diagnosis and takes the complaining organ or

part to the chosen specialist. Like doctors, they sometimes make mistakes! Often there is reference from one specialist to another without anyone supervising the general care. We could use the British system to advantage wherein the general practitioner is the health supervisor of the patient. The lack of general practitioners in some of our group clinics encourages people to be their own diagnosticians.

We hear much discussion of faulty distribution of medical services. There can be no doubt that there are great gaps in our methods of distribution. The economic situation affects the public and the profession alike. There can be no doubt that sickness, disability, and untimely death increase with poverty and the ability of the agencies to render adequate service depends largely upon some source of funds to pay for it. We should not be satisfied with a remarkable general record of good health in this country when we know that still further improvements could be made if we applied the knowledge and methods now available for control of disease. There are large numbers of our people who have no preventive treatment and no curative treatment except in great emergencies. It would require many millions of dollars to provide these services, but the amount would be small in comparison with the enormous sums now being spent to care for those suffering from diseases that could have been prevented or to conserve the resources lost through untimely death. It should be stated and emphasized that we do not yet know the causes of all diseases and that we still do not have the means to prevent all diseases. And even if we had all the means and they were offered to the public on any reasonable basis, there is no certainty that the people would avail themselves of these services. The opposition to small-pox vaccination often encountered offers an object-lesson in this regard. Some people are against one thing, some against another, and some are contrary enough to be against everything.

Anyone who takes the trouble to inquire or just to listen will soon learn that the medical profession is not generally held in high esteem by the public. The reasons for this growing antagonism are not far to seek. The quacks and faddists who attempt to enter the practice of medicine through the back door have coined the catch-term of "medical trust" for all who oppose quackery in any form. Even in some high places, organized medicine is charged with monopolistic trends. Attacks are made on the medical profession in the courts when freedom to experiment with new and questionable methods of rendering service to the sick is opposed by representatives of organized medicine.

The doctor is blamed for the high cost of sickness. He bears the brunt of criticism which is largely the result of changing economic factors. Most of the increased cost of sickness is due to the use of expensive procedures, the cost of hospitalization, the need for expensive drugs, and nursing and other services. An analysis of the costs of medical care shows that the doctor is not overpaid. As a matter of fact, he is the last to be paid. Often his bill has to be reduced in amount or even cancelled because the patient is not able to meet it.

There is widespread criticism of large professional fees required of those with higher incomes. It is probable that certain specialists make charges beyond reason for services rendered. While this is more prevalent in the surgical specialties, it is not limited to them. There are too many who capitalize on some technical procedure in which they have achieved skill. The specialist whose field of vision is confined to what he sees through a system of lenses inserted into some aperture of the body and who ignores the patient as a biological unit is a menace not only to the patient and the public but also to the standing of his profession. Sir Frederick Gowland Hopkins referred to these practices as "the mastery of technique over reason."

One reads and hears a great deal, stated in jest, about the popularity of operations. In times of distress, patients crave action and readily submit to operations recommended by those whom they trust. There can scarcely be any doubt that in this country too many operations are performed. Many specialists, highly skilled in their technics, are so incompletely trained in general medicine that they do not know the limitations of their method or the comparative value of other methods. Many unwise surgical procedures are performed by poorly trained graduates who rush from our schools into practice anxious for practical experience. It cannot be said that the profit-motive generally determines the method of treatment, but in some instances it would appear that sound judgment had wavered because of this motive. Much of the criticism by the public has been directed toward self-appointed surgeons who favor mechanistic treatment of most diseases. Why are many operative conditions more common among the rich than among the poor? Why do we have waves of popularity for operations for many diseases in which the operative mortality is higher than the natural death-rate? Sometimes when we see a neurotic patient, with many scars of previous operations, we wish that her doctors had been wiser or that they had been denied the great benefits that anesthetics and aseptic methods had brought to mankind. There is an increasing tendency among doctors to recommend exploratory operations on the assumption that the operation is relatively safe and the dangers of waiting for developments are great. Knowing the psychic and physical risks the patient takes under the circumstances, we should take a firm stand against this practice.

One of the great evils of medical practice in this country is "fee splitting" in one form or another. Untouched by codes of ethics and the influence of our great national organizations, there are sections of the country where a division of fees is almost the rule rather than the exception. It is a common practice for unethical doctors to deliver their patients wholesale to specialists for rebates which are frequently half or more than half of the fees. How can the interests of the patient be served under these circumstances? What is to be done about it? At the New Orleans meeting of the American Medical Association in 1903 and at subsequent meetings, an attempt was made to stamp out this practice. Discussions on this subject led to an exposure of the custom, which was a by-product of the lush period



of proprietary medical schools. Out of this situation arose the American College of Surgeons, founded in 1913 largely in an attempt to control this practice. Since that time, efforts have been made to curb the evil, but it flourishes largely outside the membership of national societies of specialists and probably chiefly among practitioners who are not members of the great body of organized medicine. The evil could be corrected by recognizing the services of the practitioner who discovers the condition requiring special treatment and compensating him adequately. But the patient must be made a party to the transaction. There can be no doubt that the people are becoming aware of the custom of fee-splitting, and they don't like it. During the past month two patients from widely separated places asked to be referred to ethical surgeons if special treatment were required. We should find some means to correct this situation for the honor of medicine and the welfare of the public. Let us join with all professional agencies to stamp it out. If it requires the coöperation of the public to reach those not bound by ethical standards or loyalty to any national society, then let us go directly to the people.

It should be recognized also that groups and clinics are generally organized financially upon the basis of a division of fees. Salaries for the members of the group are equalized, with some adjustment for experience or ability. The entrance of the business manager into the group has brought new problems. The psychological values of salesmanship are not lost on him. Diagnostic services are often rendered at low fees, and frequently below cost; and a profitable income is derived from surgical fees. This inculcates into the minds of the public a false set of values. It creates competitive problems for the practitioners and internists outside such groups. In large sections of the country, individual or private practice suffers. When services including diagnostic procedures (the staples) are offered at less than cost in order to attract patients who, when requiring the care of specialists, pay luxury prices for it, we are faced with a critical situation. When the practice of medicine thus enters the citadel of trade and commerce, it should be controlled by the practices and rules of trade. The regulations of the Federal Trade Commission govern the sale of commodities. A tradesman cannot lure the customer into his shop through bargain sales of "loss leaders" to reap a large profit from the incidental sale of a luxury. It should not be allowed in medical practice which, through the trends just mentioned, is being conducted on a business basis. What has been said of group practice applies equally to surgeons who make no charges or only a token-charge for diagnostic services. Such methods are too similar to those of quacks and advertising "specialists" who conduct a "come-on game" through the lure of free examinations.

Fee-splitting is not limited to doctors. Opticians and druggists sometimes divide fees or give commission to doctors, some doctors give commissions to druggists and runners and some chase ambulances. Fortunately, these exert a minor influence in the conduct of medical practice.

A few in the medical profession feel that they have a proprietary interest in patients. How much of this is motivated by the commercial interests mentioned above is difficult to determine. In small communities, this interest tends to cause unfriendly feelings among doctors, arousing jealousies and sometimes hostility.

If fees were equalized, as they may be under a scheme of social medicine, many of the defects of medical practice may be corrected. Some of those who oppose any change from the former status may do so because they know independence of action gives them license to carry on sharp methods in the matter of fee-splitting.

Another factor tending to divorce the public from reliance on doctors is the flood of proprietary medicines put up in attractive and palatable form. They are offered for sale over the counter and heralded from the air and by the printed word. Self-diagnosis and self-treatment convince people that they have no need for doctors when for a small sum they can get temporary relief for imaginary acid indigestion, constipation, a headache, a pain or a threatening cold. The obliging and less scrupulous druggist can and often does profit from this large class of people who never see the doctor until such measures fail or until it is too late for the doctor to be of real service.

Some of the major problems in medical practice are being studied intensively and progress is being made. It should be obvious that better preventive and curative service could be rendered if the best skill and facilities of the medical and allied professions could be made more generally available. This may require the establishment of groups of practitioners in easily accessible centers with hospital and laboratory facilities of the highest standards operated in close coöperation with public health officials. Doctors, dentists and other professional workers will redistribute themselves if attractive opportunities are offered. Some means must be found to pay for minimum or adequate standards of service. The public now pays for most of the free care given in the several states and should be prepared to meet a part of the costs for the borderline and low income groups. The sharing of risks through group insurance is well understood in this country, and it is through this method that the costs may be equalized. Voluntary health insurance may be preferable for those who can meet their share of the cost in the operation of the plan, but how can we expect those with marginal incomes or no income to contribute? One cannot volunteer to contribute to any scheme when he has nothing to divide. If his income does not provide the basic needs for food and shelter, these and health services must be provided under any social system. Industry may share in the expense for care of the wage-earner but not directly for his family or those not employed. The governing units now make a variable contribution to the poor and needy largely for emergency or custodial care but do little for the borderline group. It would seem to be logical that a plan of compulsory health insurance for all below a certain level of income would be desirable, with contributions by both workers and their employers. Supplementary con-

tributions should be made by counties and states with subsidies by the federal government, adjustable in amounts from each, to bring a total which will insure complete coverage for all services. The chief and to many the unsurmountable objection is the element of politics which would introduce a third party for regulation and control hazardous to the interests both of patient and physician. Such a situation already exists with respect to the workmen's compensation laws, and this is officially approved by spokesmen for organized medicine. It is to be understood that there are abuses under the operation of present industrial accident laws, although the lot of the worker has improved greatly under their provisions. The care of patients under the regulations of the Agricultural Adjustment Act is accepted in many sections of the country, and one doesn't hear of doctors refusing to accept fees for their services. In our municipal and county hospitals, local governmental service of the highest type is rendered by doctors, usually without compensation. Many doctors and others in the professional groups now on fixed salaries are rendering distinguished service. If we are motivated by a real desire for service, the profit motive should not determine the quality of our contributions. Most of us wish we never knew what fees a patient could or would pay for our services. The great contribution of groups and large clinics, private and public, is the submergence of personal aggrandizement and gain to the welfare of the patient and the group. It should be possible to select professional censors in the several states to work with representatives of the other interested parties, including business managers, economists and the public, serving for long terms and not subject to shifting political winds. The patient-doctor relationship must and under this plan could be preserved. It is a favorable sign to see some of the leaders of the profession willing to coöperate for the interests of the public as well as those of the profession. As physicians, we should insist upon control of professional services to the end that they should be of the highest quality. We are not economists or business men, nor are we very good politicians. It is too late to play politics in this matter. Too much of our time and energy has been spent already in trying to hold back or sidetrack a social tidal wave which has shaken our edifice from its foundations. We may now prepare to swim for our lives. We should ask for surf-boards and strong leaders who can steer them and take us safely to shore.

It cannot be assumed that doctors are faultless when they participate in any general plan for medical service. In some of the schemes adopted so far, it is found that a few unscrupulous doctors can find ways to increase income by performing unnecessary operations, by dressing a sore finger an unreasonable number of times or by visiting a patient with hay-fever three times a day for a month—to give but a few examples. It will be found necessary to supervise the conduct of practice to prevent the few from discrediting the work of the rest. We should put our own house in order. As one tidies up for company, we should prepare for the sociologists, economists and business managers who are invading the temple of Hygeia. It will not

do to sweep the crumbs of unethical conduct or shady practices under the rug of loyalty to members of the profession—right or wrong. It only weakens our position with the people whom we serve.

The foregoing remarks are not made to discredit our profession which, through the centuries, has attracted men with the greatest devotion and sacrifice for their fellow-men. Our weaknesses must be recognized. Self-analysis in the face of external criticism may help us to regain public support for our profession which by its nature should be most intimately associated with the lives and health of our people.

How can the American College of Physicians best serve the profession and through them the public? It can exert a great influence on American medicine by maintaining the highest quality of professional services totally free from unethical practices; it can aid in promoting the highest standards of medical education and research; and it can encourage and support continuous post-graduate education. There has never been a time when there has been so much interest in post-graduate education. The annual crop of graduates from our medical schools is increasing both in number and quality. Students are selected with great care, and their training is designed to enrich medicine through the contributions from the fundamental sciences. The thousands of young doctors leaving our schools each year are building fires behind us. These youngsters will soon overtake us, and if we cannot keep up we must get out of the way to let them go by. Perhaps this competition has spurred us to look to our laurels. There are, however, still many remote places and some not so remote where the light of improvement does not yet shine. With your permission, I should like to read some verses written by my wife with my prompting which depict the scene in many doctors' offices. These verses are entitled "The Grad from Timbuctoo" and are written after the manner of Eugene Field's "Little Boy Blue."

*The Grad from Timbuctoo*

The medical texts are covered with dust,  
Neglected and musty they stand;  
And the compound 'scope is red with rust,  
And the journals mold, near at hand!

Time was when the favorite texts were new  
And the 'scope had its daily wear  
'Twas then that the Grad from Timbuctoo  
Left school—and put them there.

"You'll be right here when I've time," he said,  
"And after my rounds are through!" . . .  
Then he hurried off, at last, to bed  
And dreamt that his plans came true.

But as he was dreaming an urgent song  
Woke the Grad from Timbuctoo . . .  
The work came thick, and the money fast,  
He had all that he wished to do.

And always waiting, right close at hand  
While the dust and the rust grew more  
Were texts and journals and microscope  
With the latest of medical lore;

Aye, faithful to Timbuctoo they stood  
Each in its given place,—  
Just waiting the touch of a searching mind,  
And the smile of a willing face;

They wondered as waiting the long years through  
In the dust, without any care  
Why that Grad from Timbuctoo  
Ever got them and put them there!

Then gradually, as the years slipped by,  
The Grad felt his prestige fall,  
And he realized with a sudden pang  
That he hadn't "kept up" at all;

He looked askance at the rust and dust  
And the stack of journals high  
And he knew in his heart he'd never catch up  
No matter how hard he'd try!

\* \* \* \* \*

Are you like the Grad from Timbuctoo  
Who failed in its standards high?  
Will you, as the years go racing along,  
Let the chance to "keep up" slip by?

If so, you'll wonder, while sitting alone  
In the dear old office chair,  
Why other doctors are busy as heck  
And you are just sitting there!

—Dorothy Fish Kerr,  
September, 1938.

Except in a few of our leading medical schools, no well designed plans have been developed to keep the doctor abreast of advances in his field. Many of our medical schools are coöperating with state and county societies in offering refresher courses either at the schools or in centers convenient for large numbers of the profession. Many organizations, such as the American Medical Association, serve their own members and others through their annual meetings. Some, such as the Interstate Postgraduate Medical Association of North America, and several patterned after this organization, bring outstanding teachers and others to large groups of the profession for short periods. In Boston under the leadership of Dr. J. H. Pratt a plan has been instituted to bring general practitioners to the hospital for periods of instruction, and to provide substitutes so that the interests of both patients and doctors will be served. This seems to be a step in the right direction. The doctor at the cross-roads needs stimulation and continued instruction to keep abreast of the rapid changes in medical practice. Since the

practice of medicine is primarily personal and individual, the doctor cannot be absent or unavailable except for brief periods. If a way could be found to keep him up-to-date by a system of substitution or by making instruction available near his home for a few hours a week, much good could be accomplished. Most doctors would be willing to pay for this instruction. In order to insure the highest type of service to the people, it may be wise to require licentiates of the State Medical Examining Boards to show continued proficiency by limiting the years for which a license is granted. This would, of course, presuppose adequate opportunities for instruction and a system of grading through some method of examination or other suitable device.

Continued instruction for the recent graduate is well recognized as a valuable means to proficiency in clinical medicine. Many graduates continue instruction for one or more years in special fields after the intern year, the need for which is taken for granted by most graduates and which is required by many medical schools. The American College of Surgeons is actively engaged in a program of inspection and certification of hospitals qualified to offer graduate training in their special fields. The American College of Physicians is now considering a plan of coöperation with all existing agencies to the end that adequate graduate instruction in the special fields of general medicine shall be provided. The examining boards for the certification of specialists are setting up standards and outlining the content of schedules of instruction that will be acceptable for qualification. This is causing some concern to administrators of hospitals and medical schools, and in many instances is unfair to recent graduates. The American Board of Internal Medicine allows some freedom to those intending to qualify for certification. The stand is well taken that we should not be concerned with the method by which proficiency is gained. The product is what we should examine.

The problem of keeping up after the many hurdles are passed is of great concern to the American College of Physicians. Our annual session offers unusual opportunity to hear what is new and important. Our programs are developed with great care to bring distinguished contributors from all fields of medicine before you. Our special short courses are offered to meet the demands of our members. As we gain in experience we shall be able to utilize more fully the resources of our medical schools where generous coöperation is ours for the asking. Through these means and through the medium of the *ANNALS OF INTERNAL MEDICINE*, some of the interests of our members are being served. When other objectives of the College are defined, it may be taken for granted that they will be based upon a desire to elevate the standards of medical practice, education and research, and through such improvements to serve humanity.

There has been some discussion about educating the public in matters of health. There has never been a time when the people have been so interested in science and medicine. Announcements of discoveries are being made through all the mediums of publicity. The people have no means of dis-

tinguishing the good from the bad, and fraud and deceit thrive in minds accustomed to hearing of modern miracles in these fields. Some decry any effort to pass on the results of experiment and practice to the people, but there can be no valid objection to general education along proper lines. The people need to know how to use the services of doctors and others contributing to the purposes of sound health; how to choose a good doctor; and how to meet emergencies until the doctor comes. It would be of great educational value if the United States Public Health Service would undertake to put into the hands of every family a book or pamphlet on matters of health. Frequent revisions could keep the contents up to date. The editorial board should include authorities in all fields of medicine and other professional groups, but they should remain anonymous. In the several states a list of qualified general practitioners and specialists could be included for guidance of the people. The contents should include information on general health and how to maintain it. Prenatal and postnatal care of the mother and child should be discussed. For the life emergencies, there should be instruction on measures to take until the doctor comes, and how to coöperate with him and others afterward. Hazards of life and health which can be avoided should be made known to the people. If properly presented, this instruction would reduce the use of nostrums and cure-all methods of treatment which are now a great source of profit to unscrupulous promoters, and may be injurious or result in loss of precious time.

This is but a brief discussion of the many problems confronting us as a profession. The great majority of our colleagues are inspired primarily with a desire for service. Medicine must always remain the keystone in the arch of service, supported by *les voussoirs* of public health and preventive medicine, dentistry, nursing, social service, technical service and hospital management, and based upon the piers of research and education. Through this arch the public shall pass to a fuller realization of the value of scientific achievement and come to have a better appreciation of the motives which inspire us all.

The American College of Physicians welcomes to its fellowship tonight many who have achieved the merit of high professional attainment. It is our firm conviction that during the period of changing ideologies in medical practice, you will help us to hold aloft the torch of service. May we all cling to the motive that first led us to study medicine: the desire to be of some service to suffering humanity! And as we go our rounds, may we always repeat our salutation when we become doctors of medicine:

We who are about to serve salute you.

Servimus te Salutamus.

# CHRONIC IDIOPATHIC HYPOPARATHYROIDISM; REPORT OF SIX CASES WITH AU- TOPSY FINDINGS IN ONE \*

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"CHRONIC idiopathic hypoparathyroidism" is a disease identical with postoperative hypoparathyroidism except that the agent which has interfered with the parathyroid function has not been established. Certain criteria must be fulfilled before the diagnosis can be made. The serum calcium level should be low, but a more important point is that the serum inorganic phosphorus level should be increased.<sup>1, 2, 3</sup> Renal insufficiency, however, should be ruled out as a cause of the hyperphosphatemia. The bones should be normal by roentgenograms in order to rule out rickets or osteomalacia as the cause of the hypocalcemia. The teeth, however, as might be expected from the work of Erdheim,<sup>4</sup> may show characteristic developmental defects if the disease started before dental maturity.<sup>5</sup> The signs and symptoms of tetany should of course be present, but they serve merely to call attention to the tetany and do not help in determining its type. Cataracts and trophic changes of the nails may be present but are not specific for idiopathic hypoparathyroidism.

Tetany is encountered in a number of diseases in no way related to underfunction of the parathyroid glands. These diseases may be divided into two groups: (1) those with a low serum calcium level and (2) those with alkalosis. Diseases other than hypoparathyroidism responsible for a low serum calcium level are rickets, osteomalacia (including "Arbeiter-tetanie"), steatorrhea (including sprue), chronic diarrhea and chronic renal insufficiency. Alkalosis with resulting tetany is seen in hyperventilation, persistent vomiting, following the administration of certain drugs, etc.

In this paper the clinical data from six patients with chronic idiopathic hypoparathyroidism are presented. Eight more cases which satisfy our diagnostic criteria are abstracted from the literature. The study is concerned not with the effect of the hypoparathyroidism on the body but with the possible cause of the parathyroid pathology. It is obviously a matter of considerable interest what agent could lead to a deficiency of all four parathyroid glands. The case histories are given in the hope that as more cases are recorded some common denominator will appear. One of the seven patients here reported died. This case is presented in more detail and

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the autopsy findings are included. The possible significance of the observed parathyroid gland changes is discussed.

### EIGHT CASES FROM LITERATURE

If all the factors capable of producing tetany are kept in mind, one finds that most of the cases reported in the literature as "idiopathic hypoparathyroidism," "idiopathic tetany," "essential tetany," etc. are not admissible as proved cases of idiopathic hypoparathyroidism. Careful search of the literature, however, did reveal the following eight cases in which the diagnosis of "chronic idiopathic hypoparathyroidism" seems reasonably justifiable. Transient hypoparathyroidism in new born infants is not considered here (v. case of Pincus and Gittleman<sup>7</sup>). Only those data which might give a clue to the etiology of the disease are recorded.\*

Beumer and Falkenheim,<sup>8</sup> 1926. Three and a half year old boy. Symptoms of tetany for one year. All the signs of tetany on admission. Past and family histories irrelevant. Cod liver oil had been taken without avail. Blood serum calcium, 4.3 mg. per 100 c.c.; blood serum phosphorus, 9.4 mg. per 100 c.c. Roentgenograms showed no evidence of rickets.

Liu,<sup>9</sup> 1928. Forty-six year old Chinese male. Symptoms of three years' duration. Signs of tetany on admission. Serum calcium, 6.0 mg. per 100 c.c.; serum phosphorus, 7.2 mg. per 100 c.c. Blood chlorides and CO<sub>2</sub>, normal. He had had some diarrhea. Ascaris and hookworm ova were found in his stools. Urine analysis, normal. Roentgenograms of bones, normal. Past history, negative. The patient did not improve with cod liver oil or sunlight. Parathormone gave but temporary relief.

Albright and Ellsworth,<sup>10</sup> 1929. Fourteen year old Italian boy with symptoms of tetany since age of eight. Past history of measles and chicken-pox (aged 5). Tonsillectomy (aged 8) just prior to onset of tetany. One attack of carpopedal spasm had been precipitated by a gastrointestinal upset and another by an upper respiratory infection. Physical examination showed classical signs of tetany, teeth in poor condition, early cataracts, enlarged epitrochlear glands, and a palpable spleen (on a later admission). Wassermann reaction, negative. White and red blood corpuscle counts, normal. Basal metabolic rate, minus 6. Plasma calcium, 5.3 mg. per 100 c.c.; plasma phosphorus, 10.8 mg. per 100 c.c. CO<sub>2</sub> combining power of blood, 52.4 volumes per cent. Whole blood chlorides, 80.3 m. eq. per liter. Urine analysis, normal. Roentgenograms of bones, normal.

Leopold and Jonas,<sup>11</sup> 1932. Male, aged 38, with symptoms of tetany of six months' duration. Past history negative except for scarlet fever in childhood. Blood calcium, 5.8 mg. per 100 c.c.; blood phosphorus, 5.4 mg. per 100 c.c. Blood CO<sub>2</sub>, 74 volumes per cent. Patient followed for four years, during which time blood calcium usually was about 6.4 mg. per 100 c.c. and blood phosphorus about 6.0 mg. per 100 c.c.

Cantarow,<sup>12</sup> 1932. Female, aged seven. Attacks of "spasticity" and convulsions since age of three and a half. Constipation and diarrhea for 18 months before entry. Past history of a green stick fracture of right fibula at 18 months, a similar fracture of left fibula at 19 months, and tonsillectomy at three and a half years. No history of rickets. Treatment with vitamin D had been without benefit. Examination showed classical signs of tetany, coarse hair, and dry, thick, puffy skin. Serum

\* The two cases briefly described by Bauer, Marble, and Claffin<sup>6</sup> in 1932 are included in the seven cases herein described.

calcium, 4.8 mg. per 100 c.c.; serum phosphorus, 10.4 mg. per 100 c.c. Blood  $\text{CO}_2$ , 56 volumes per cent. Basal metabolic rate, not reported. Roentgenograms: suggestive of enlargement of thymus; bones normal.

Cantarow,<sup>12</sup> 1932. Female, aged six. Illness started three years previously with attacks of dyspnea, cyanosis, retraction of the abdominal wall, and vomiting, ushered in by a peculiar cry. No history of acute infectious or rickets. Obstinate constipation and delayed dentition had been noted. Vitamin D and calcium treatment had been without effect. Examination showed classical signs of tetany, sparse coarse hair, and coarse thickened skin. Serum calcium, 4.2 mg. per 100 c.c.; serum phosphorus, 11.8 mg. per 100 c.c. Blood  $\text{CO}_2$ , 65 volumes per cent. Basal metabolic rate not reported.

Kirklin and Childrey,<sup>13</sup> 1936. Female, aged 19, who had had tetany since seven. Onset followed measles which was complicated by nephritis. Examination showed classical signs of tetany and bilateral cataracts. Serum calcium, 5.2 mg. per 100 c.c.; serum phosphorus, 8.2 mg. per 100 c.c. The urine analysis and the renal function were entirely normal and the blood urea nitrogen was 32 mg. per 100 c.c.\*

Arnold and Blum,<sup>14</sup> 1936. A 38 year old housewife. She had had typhoid fever at 15, an appendectomy "in 1912" which had not relieved her right lower quadrant pain, and colitis with 11 weeks of hospitalization "in 1917" with a recurrence "in 1922." Her general health had declined for seven years before she was seen by the authors. In addition to the signs of tetany she showed tenderness over the sensory nerves, poor teeth, a dry and scaly skin, and thin hair. Serum calcium, 5.4 mg. per 100 c.c.; serum phosphorus, 6.1 mg. per 100 c.c.

### CASE REPORTS

*Case 1.* B. W., a Russian Jewish tailor, entered the Massachusetts General Hospital July 10, 1926 at the age of fifty-two. He gave a history of having suddenly fallen in the street nine months previously, at which time he did not lose consciousness, but could not arise unassisted because of stiffness, contraction, and numbness of his arms and legs. For 10 weeks prior to admission he had noticed increasing stiffness and cramps of the muscles of his hands, arms, feet, and legs. Three weeks before admission he had had a severe attack associated with loss of consciousness, for which he had been treated at the Boston City Hospital. Since then he had had persistent pains in the shoulders, more marked on the left.

The family history was non-contributory. He knew little about the medical histories of his antecedents. His wife and four children were healthy.

The patient did not recall any previous illnesses. There were no other symptoms than those referable to the neuromuscular system.

Physical examination showed a slightly under-nourished middle aged man with extremities in carpopedal spasm. The Trousseau and Chvostek signs were both positive. The initial blood pressure was 88 mm. of mercury systolic, and 70 diastolic, but later observations were always normal. The temperature, pulse and respirations were normal.

Routine urine and blood studies were normal. The nonprotein nitrogen of whole blood was 64 mg. per cent, the sugar 95 mg. per cent, and  $\text{CO}_2$  combining power 71.8 volumes per cent, and the serum chlorides 111 m. eq. per liter. (The nonprotein nitrogen two weeks later was within normal limits, and this was the case on repeated subsequent determinations.) The basal metabolic rate was minus 1 per cent. The serum calcium was 5.1 mg. per 100 c.c.; the serum phosphorus 7.3 mg. per 100 c.c. At a subsequent admission a sugar tolerance test was found to be normal, and the blood cholesterol was 154 mg. per cent. Roentgenograms of the bones were normal;

\* Personal communication from Dr. Oren L. Kirklin.

those of the teeth showed multiple root abscesses. Spinal fluid examination at a much later date gave normal findings. A gastric analysis showed low free acidity.

This patient has been followed since his first admission. The treatment of the hypoparathyroidism is beyond the scope of this paper. Suffice it to say that whenever treatment was omitted the symptoms recurred and the serum calcium and phosphorus levels returned to approximately the values cited above. Cataracts formed and the lenses were removed. The abscessed teeth were removed without any change in the underlying condition. On his tenth and latest admission, in January 1937, his serum phosphatase was found to be 2.8 Bodansky units, his serum calcium 7.1 mg. per 100 c.c., and his serum phosphorus 4.8 mg. per 100 c.c.

*Case 2.* D. B. entered the Out-Patient Department November 20, 1929 at the age of 13, complaining of "fits" at weekly intervals for four years. A diagnosis of "idiopathic epilepsy" was made and the patient was treated with phenobarbital. The attacks continued. The patient was referred to the Ear Clinic because of bilateral chronic otitis media which antedated the onset of the "fits" by about a year. Roentgenograms showed a chronic sclerosing mastoiditis.

On January 8, 1933, the patient was admitted to the hospital for complete study. The history at that time revealed that she had had repeated attacks of stiffness and tingling of the hands and feet for a period of 10 years. These attacks varied in frequency from one every three or four months to five or six attacks a day, being especially frequent after a respiratory infection. Additional symptoms were stiffness of the jaws and rigidity of the whole body. In some of the attacks the patient became dizzy, felt a gripping sensation in the throat, and became unconscious for three or four minutes.

The parents were healthy; three siblings were living and well; and there were no familial diseases.

The past medical history disclosed that she had had measles, chicken-pox, and whooping cough in childhood. Since eight she had had recurrent bilateral otorrhea. Shortly after the onset of this condition a tonsillectomy and adenoidectomy had been performed. Her diet had been adequate in every respect. The menarche had taken place at 13, the menses occurring irregularly every four to five weeks.

Physical examination showed a well developed and nourished 17 year old girl with carpopedal spasm. The Chvostek and Trousseau signs were strongly positive. Both ears were draining. The lenses were clear to the slit lamp examination. The temperature was 98.6°, pulse 80, respirations 25. Examination was otherwise negative. However, on a subsequent examination (January 18, 1934) she had an enlarged liver and a palpable spleen.

Laboratory examinations showed the urine, blood counts, and stools to be normal. The Hinton test for syphilis was negative, the fasting blood sugar 89 mg. per cent, and the nonprotein nitrogen 23 mg. per cent. The serum calcium was 7.0 mg. per 100 c.c. and the serum phosphorus 7.0 mg. per 100 c.c. Additional laboratory data obtained at a subsequent admission showed a normal sugar tolerance curve, a serum phosphatase of 2.5 Bodansky units, a whole blood CO<sub>2</sub> combining power of 58.4 volumes per cent, and three basal metabolic rates of minus 21, minus 13, and minus 21 respectively. A roentgenogram of the chest was normal. The vertebrae, pelvis, femora, and skull were all normal by roentgen examination. Roentgen-rays of the teeth showed the upper third molars unerupted and malposed. The premolars were approximately a centimeter shorter in length than they should be, and the roots were stubby. These dental findings will be discussed elsewhere.<sup>5</sup>

The patient has been followed since. Except when under treatment the condition has remained stationary with about the same degree of hypocalcemia and hyperphosphatemia. A tissue culture of a parathyroid tumor from another patient

was transplanted into the patient's left axilla without any permanent improvement. The patient subsequently became pregnant.

*Case 3.* P. R., a 14 year old American schoolboy of Italian descent, entered the hospital January 24, 1935 with a two months' history of "painful twitchings" of the muscles. Shortly after his admission he had an attack of unconsciousness. After a second similar attack 10 days later the diagnosis of tetany was made. For only two weeks had he been unable to do his work as a newsboy.

The past history showed that in infancy he had been in a hospital for a condition on the back of the head which had healed leaving a scar. Up to two years before entry he had had nose bleeds about once a month. No childhood disease or other previous illnesses were remembered.

His mother was living and well at forty. His father died of a heart attack at thirty-nine. Six siblings were living and well. There was no history of a similar disease in the family.

Physical examination showed a thin, undernourished, 14 year old boy with positive Chvostek and Trousseau signs. The teeth were in poor repair. The blood pressure was 120 systolic and 90 diastolic. The temperature was 99° F., pulse 90, and respirations 20.

Laboratory examinations showed normal urine analysis, normal blood counts, a negative Hinton test for syphilis, serum calcium 4.7 mg. per 100 c.c.; and serum phosphorus 12.9 mg. per 100 c.c. The spinal fluid was negative to the routine tests including the Wassermann.

Roentgenogram of the chest was negative. Roentgenograms of the right wrist and elbow showed normal epiphyses, and bone structure. Roentgenograms of the teeth showed changes which will be described elsewhere.

While in the hospital the patient had *rubella*. This was associated with an eosinophilia of 20 per cent, and occurred before any parathormone was given. The patient later developed erythema nodosum of the legs.

The patient has been followed since. Various forms of therapy have been tried. Without therapy the condition always returned to that seen at the time of the first admission. Cataracts developed for which both lenses were removed.

*Case 4.* W. C., an American school boy, was admitted for the first time March 5, 1936 at the age of sixteen. He gave a four year history of attacks of painless involuntary spasm of the hands and feet associated with a "wooden feeling" or sensation of numbness. On several occasions he had fallen down and had been unable to rise until the spasm had passed off. Running or other forms of exertion precipitated the attacks. Severe attacks had occurred only in the winter.

The mother, aged 58, had hypertension. The father, aged 60, had bronchial asthma and was unable to work. Four brothers and four sisters were living and well. One brother and one sister died quite young of unknown causes. One sister had had rheumatic fever.

Past history was negative except for mumps, chicken-pox, and a tonsillectomy at the age of five.

The physical findings of note were slight undernutrition, opacities in both lenses, and a strongly positive Chvostek sign. Blood pressure was 130 systolic and 80 diastolic.

Laboratory studies showed his urine analysis, blood counts and stools to be normal. The Hinton test was negative. The blood non-protein nitrogen was 23 mg. per 100 c.c.; the basal metabolic rate, minus 4 per cent; the phenolsulphonephthalein renal function test, normal. The serum calcium was 6.1 mg. per 100 c.c., serum phosphorus 10.2 mg. per 100 c.c., serum phosphatase 15.4 Bodansky units. Roentgenograms of the skull showed areas of calcification on both sides interpreted as calcification in the choroid plexuses. The sella turcica appeared normal. Roentgenograms

of the long bones, chest, and kidney region were interpreted as being normal. Arterial blood studies by Dr. John H. Talbott showed  $\text{PCO}_2 = 41.0$  vol. %, Tot.  $\text{CO}_2$  of true plasma  $= 58.8$  vol. %,  $\text{pH}_s = 7.41$ . These values were normal and ruled out alkalosis.

The patient has been followed since but no additional data concerning the etiology of the disease have been obtained. When not receiving treatment he quickly reverts to the state observed at the time of entry.

*Case 5.* The following case history was very kindly supplied by Dr. Roy F. Farquharson from the Toronto General Hospital.

The patient, a Russian Jew of 44, entered the Toronto General Hospital in February 1929, because of symptoms of tetany. His illness started two months before admission at which time he and other members of his family suffered an acute illness which was diagnosed as influenza. Symptoms consisted of malaise, fatigue, generalized aching, and a hyperpyrexia of  $100^\circ$  F. and over. The symptoms of tetany started four days following the onset of this illness and persisted until admission.

On physical examination he presented the typical picture of a patient with fairly severe tetany. Otherwise the examination was not remarkable except for dental sepsis.

Roentgenograms of the sinuses showed some involvement of both antra. The roentgenograms of the bones were not remarkable except for some osteoarthritis of the spine.

He was seen from time to time up to January 1935. The tetany persisted. The serum calcium was always low—4.4 to 7.0 mg. per 100 c.c., and the serum phosphorus was always high—6.2 to 7.3 mg. per 100 c.c. His urine examinations were always entirely negative.

#### CASE WITH AUTOPSY

*Case 6.* A. P., a boy of five, first entered the hospital October 5, 1926 with a history of convulsions once or twice a week for nine months.

The family was American; the parents were healthy, two siblings aged one and three years were normal; and no family diseases were known.

The patient was born prematurely at  $7\frac{1}{4}$  months. The mother was a nullipara and labor had lasted 16 hours, being terminated by instrumental delivery. The infant weighed five lbs. but was healthy, and was breast fed for 10 months. Dentition began at two months and walking at one year. The patient had pertussis at two and measles at four years.

The present illness began approximately one year prior to entrance at which time he developed pains in the right foot with some degree of inversion. Shortly thereafter the patient's parents noted that he handled a fork or spoon awkwardly. Nine months before entry he had the first convulsion. Thereafter, these occurred about once a week, increasing to twice a week during the month prior to entry. A typical convulsion was described as starting with abdominal pain followed by general tonic rigidity of the body and extremities with retraction of the head and cyanosis. Events during the attack were lost from memory. For 10 months his appetite had been poor.

Physical examination showed red marks on the face suggesting impetigo scars, dental caries, pyorrhea, palpable epitrochlear lymph nodes, and absent knee jerks. The temperature was  $98^\circ$  (R), pulse 80 to 110, respirations 20 to 35 per minute.

Laboratory tests showed the urine, blood counts, stool, and spinal fluid to be normal. The Wassermann and tuberculin tests were negative, and the Schick test positive. Roentgenograms revealed no abnormalities of the skull and no enlargement of the thymus region.

The patient was discharged two weeks after admission to the Out-Patient Department with a presumptive diagnosis of epilepsy, but one month later was readmitted with the history that since discharge the convulsions had continued at intervals

of a week or two, and that at night he had breathed with a crowing sort of inspiratory sound. The stiffness and spasm of his hands and feet had increased.

This time the patient showed exaggerated deep reflexes, carpopedal spasm, Chvostek and Trousseau's signs. Again the urine analysis, blood counts, Wassermann reaction, and spinal fluid were normal. A sugar tolerance test was normal. The serum chlorides were 103 m.eq. per liter, and the  $\text{CO}_2$  combining power 59.5 volumes per cent. The tuberculin test had become positive in 1:1000 dilution. The serum calcium was 5.2 mg. per 100 c.c., and the serum phosphorus 12.0 mg. per 100 c.c. Roentgenograms of the skull, sella turcica, and hands were normal. Blood cholesterol was 256 mg. per 100 c.c. The basal metabolic rate was minus 8 per cent. Electrocardiogram showed sinus arrhythmia.

The patient was given 1 gm.  $\text{NH}_4\text{Cl}$  daily and in 11 days the tetany had stopped. The  $\text{CO}_2$  combining power was lowered to 48 volumes per cent. Following this he received 2 c.c. of 50 per cent  $\text{CaCl}_2$  and  $\frac{1}{2}$  grain desiccated thyroid daily. No further convulsions occurred. He was discharged June 16, 1927 on this regime.

During the next year and a half he remained comfortable while on this treatment, but any cessation of it resulted in severe attacks of tetany.

He was admitted for the third time February 18, 1929. The findings were as before except that following parathormone administration he developed an eosinophilia of 8 to 11 per cent. The patient was very thoroughly studied for nearly five months, during which time the effect of parathormone, ammonium chloride, and irradiated ergosterol was evaluated. The best results were obtained with a combination of  $\text{CaCl}_2$  and irradiated ergosterol. On July 6, 1929 he was discharged on the following regime: 50 per cent  $\text{CaCl}_2$ —drams 1, three times daily; Vigantol—5 drops daily; thyroid extract (Armour)—gr. 1 daily; and high calcium diet. The patient did very well on this regime but gradually discontinued one measure after another until finally his only treatment was 50 per cent  $\text{CaCl}_2$  1 dram twice a day. For five years he managed fairly well without other treatment. During this time he had one or two convulsions a year, and noted stiffness of the hands and feet about once every two months. He noted increasing constipation during this period.

On the final admission, September 23, 1934, he complained of abdominal pain and persistent vomiting of two to three weeks' duration. He was found to have otitis media and to be very toxic, with a swinging temperature up to  $104^\circ$ . After drainage of the ear he showed a poor clinical and leukocytic response. Septicemia and metastatic abscesses of the back and a purulent arthritis of the knee supervened. He died of sepsis October 11, 1934.

#### POSTMORTEM EXAMINATION.

Exclusive of the changes found in the parathyroids, the significant necropsy findings were subcutaneous abscesses of the back and thigh and septic arthritis of both knees. Postmortem blood cultures showed *Streptococcus hemolyticus* and *Staphylococcus aureus*.

Grossly, all four parathyroids were easily demonstrated. They were normal in size, each measuring approximately 6 by 3 by 2 millimeters. The surfaces were smooth and very pale brown in color. There was no question in the minds of the many observers that the glands demonstrated were characteristic of parathyroid tissue. Two of the glands were fixed in Zenker's fluid, one in 10 per cent formalin and one in absolute alcohol.

Microscopically, all the parathyroid parenchyma in all four glands was replaced by fat cells (figure 1). The normal architecture of the gland was still present, there being a well-outlined fibrous connective tissue capsule. The pericapsular tissue was composed of fat cells in which were scattered large vessels filled with red blood cells,

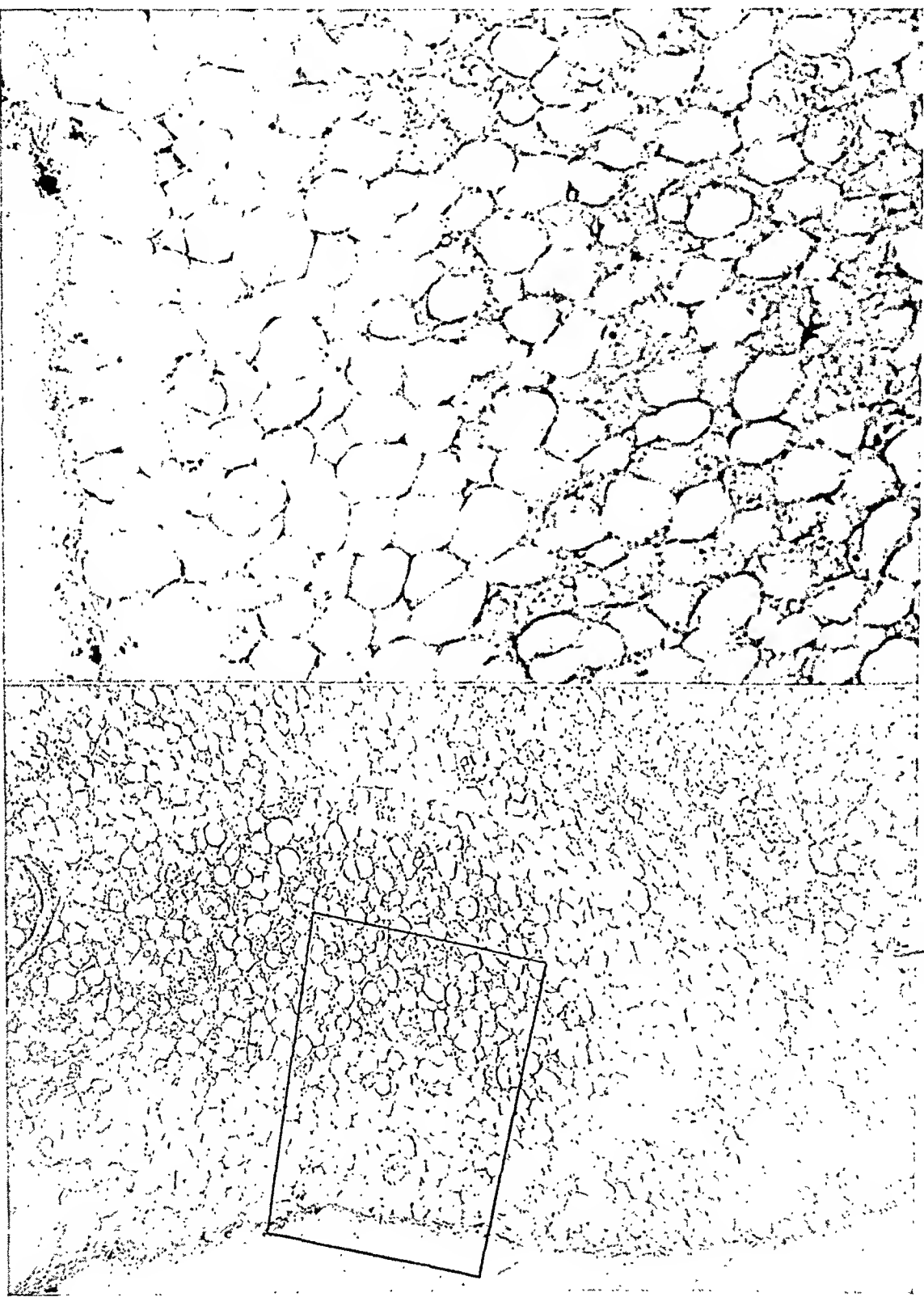


Fig. 1. High power photomicrographs of parathyroid tissue from Case 1.

a picture that is seen in the normal gland. The appearance of the fat cells in and about the peripheral fifth of the gland was quite different from that seen in the central four-fifths. In this outer zone each fat cell was outlined by a sharp, thin, acidophilic membrane and was contiguous to several similar cells, the intervening stroma being practically absent except for an occasional small, flattened, basophilic cell. This fat tissue was in all respects similar to that deposited between parathyroid cells in the normal adult gland. The cells were all equal in size and no parathyroid epithelial cells could be identified between them. The remainder of the gland was composed of fat cells of varying sizes with definitely more intercellular stroma. This increased stroma was found to be composed for the most part of cells containing much smaller fat droplets. The majority of these cells were about the size of a normal parathyroid cell; some, indeed, contained very tiny droplets similar to those often seen within the normal chief cell. In addition there were between the larger fat cells irregular deposits of light, eosinophilic, amorphous material, a finding that is occasionally seen within cystic spaces of normal parathyroid glands. The connective tissue cells in the stroma were definitely increased. The vascular supply of the stroma was similar to that observed in the normal gland.

It was difficult to determine whether any of the cells observed were normal parathyroid cells. There were scattered single cells which closely resembled chief cells, but the fact that they occurred singly made it extremely difficult to be certain that they were. Occasional dark oxyphil cells, such as one observes in the normal gland, were seen close to the stroma. All the fat cells described stained with Scharlach R. No glycogen granules were seen.

It was thought that the above described findings showed definitely that the specimens studied were the remains of the parathyroid glands and not pieces of fat mistaken for parathyroid tissue, an objection that might be raised. The glands were identified and removed by one of us (B.C.) who had previously removed and studied the glands from approximately 200 necropsies. It did not seem possible that an error in recognition could have been made in the case of all four glands. The presence of a definite capsule, the distribution of the fat cells, the possible presence of a few chief cells and the finding of definite dark oxyphil cells would seem to be sufficient evidence to prove that the specimens examined were parathyroid glands. The absence of glycogen was to have been expected in non-functioning cells.

All the glands of internal secretion were examined but no other marked abnormalities were noted. There was a diffuse lymphocytic infiltration of the pancreas. It was thought that there was a diffuse, moderate increase in the basophilic cells in the pituitary.

## DISCUSSION

The clinical findings in 14 cases (eight from the literature and six here reported) of idiopathic hypoparathyroidism have been reviewed. The autopsy findings of fatty replacement (?) of the parathyroid epithelial cells in one of our cases have been presented. A careful search of the literature has revealed no similar example.

Increase of the interstitial fatty tissue of the parathyroid glands has long been known to occur with age (Benjamins,<sup>15</sup> Erdheim,<sup>16</sup> and von Verebely<sup>17</sup>). It is the experience in this hospital that fat cells begin to appear in the normal parathyroid after puberty and increase in number up to middle age. A gland from an individual 40 years of age usually has a fat content between 30 and 50 per cent. As has often been pointed out it is inexact



and loose nomenclature to refer to these changes as "fatty degeneration." A more suitable term probably is "fatty replacement." The situation may be quite analogous to that in the bone marrow, where the fat cells merely fill up the space not taken by the hematopoietic tissue or give way to that tissue when there is hyperplasia. It is not at all certain, however, that the changes in the case here described represent the limiting degree of this fatty replacement. It is rather believed, on the other hand, that some obscure degenerative process must have been present as well. The pathology is not to be confused, furthermore, with what Herxheimer<sup>18</sup> calls "lipomatosis of the parathyroids" which is nothing more than a fatty infiltration of the stroma of the glands, such as may occur in any organ, especially in those of an obese individual.

The findings in another case which has been recently autopsied at the Massachusetts General Hospital and which will be reported in detail by Castleman and Hertz<sup>19</sup> are pertinent to the above discussion. The patient was a woman of 48 with clinical evidence of marked hypothyroidism and hypopituitarism. Hypoparathyroidism was not suspected and so blood calcium studies were not done. Autopsy showed sclerosis of the anterior pituitary and atrophy of all the endocrine glands. The parathyroid glands showed almost complete replacement of the epithelial cells by fat cells (figure 2). This was simple "fatty replacement" due to epithelial atrophy. There was no suggestion of a degenerative process.

It is impossible, of course, to know whether all the cases of idiopathic hypoparathyroidism will have the same pathology. The following review of lesions found in the parathyroid glands which might cause hypofunction seemed of interest. No other case of demonstrated idiopathic hypoparathyroidism with autopsy findings has been found.

According to Herxheimer<sup>18</sup> no case of complete aplasia of the parathyroids has been recorded. Hypoplasia, however, has been described by Boettiger and Wernstedt<sup>20</sup> in a four month old infant dying of tetany, in whom the parathyroids were so minute they could be found only by serial sections of the tissue of the neck. Haberfeld<sup>21</sup> described hypoplasia of the parathyroids in a 25 year old man dying of typhoid fever who had tetany during his illness. He interpreted this to mean that the patient had enough parathyroid tissue to prevent tetany until the stress of an acute infection occurred. Atrophy of the parathyroids, without some obvious cause such as hemorrhage, fibrosis, syphilis, and so forth, has not been reported.

A large number of focal lesions has been described which could hardly be considered as an adequate explanation of chronic hypoparathyroidism. These include hemorrhages,<sup>22, 23, 24, 25, 26</sup> bacterial emboli,<sup>23, 24</sup> cysts,<sup>18, 24</sup> and malignant invasion.<sup>23, 27</sup> Various tuberculous lesions<sup>15, 27, 17, 28, 24, 29</sup> are on record, but little importance can be attached to them. Rheumatic<sup>30</sup> and suppurative parathyroiditis<sup>31</sup> are probably of academic interest only.

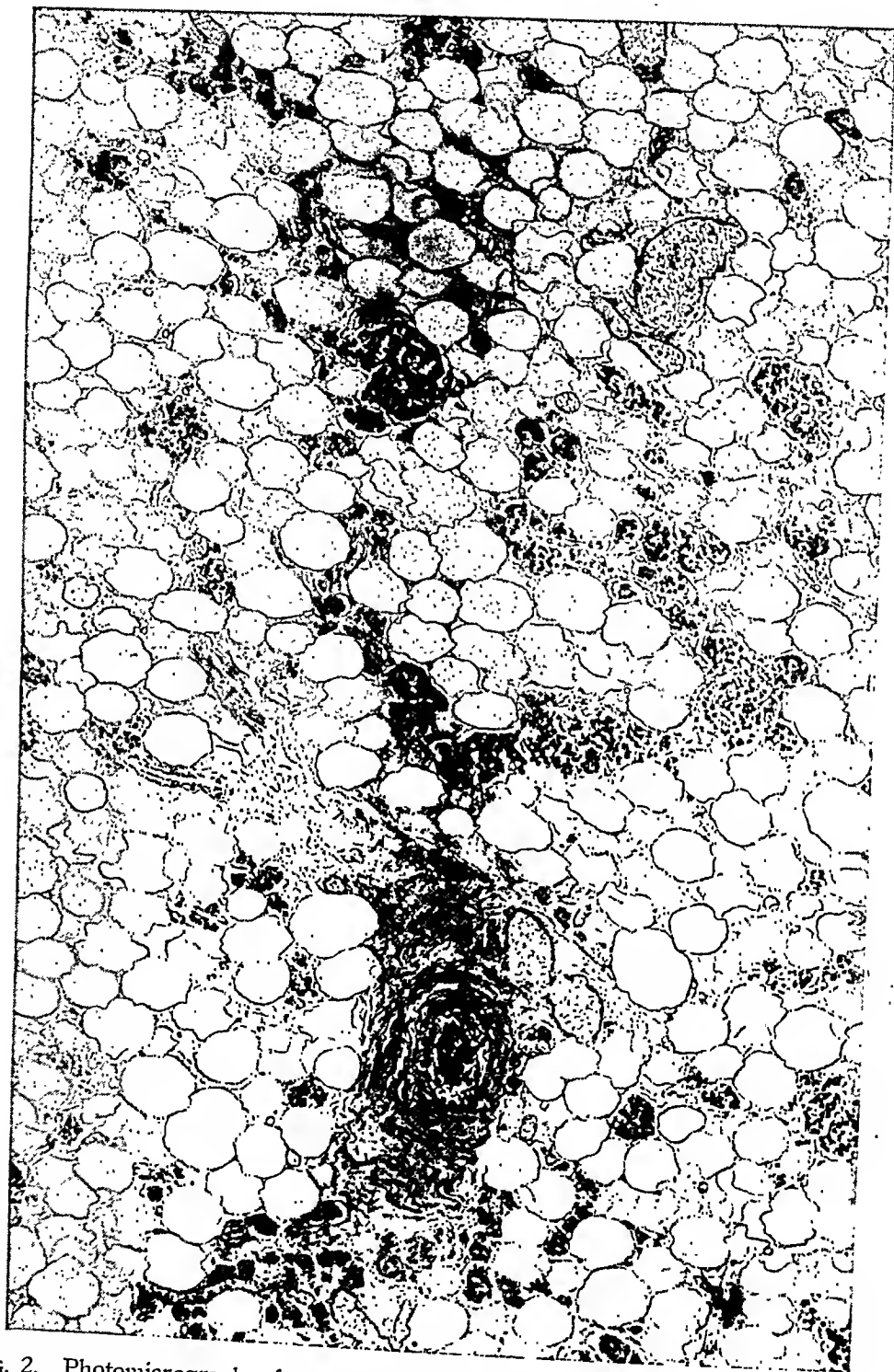


FIG. 2. Photomicrograph of parathyroid tissue from case of Hertz and Castleman. Note few remaining islands of epithelial tissue, in contrast to figure 1 where no epithelial tissue is present.

The evidence for syphilis is slightly more impressive. Haberfeld<sup>21</sup> described a case of a six weeks old infant with congenital syphilis in whom the parathyroids showed hemorrhages, old blood cysts and atrophy of the parenchyma. No mention was made of whether or not tetany had been present. Lindemann<sup>32</sup> also described what he interpreted as syphilitic atrophy. Kraus<sup>33</sup> in a newborn infant with syphilis reported the finding in the parathyroids of a chronic productive interstitial inflammation including parenchymal atrophy, lymphocytic and larger mononuclear infiltration. Langeron<sup>34</sup> and his collaborators described the case of a 47 year old mason who had had recurrent tetany for five months before death. The blood calcium was low. At autopsy gummata of the lungs were found. The two external parathyroids were examined and found to be yellower and larger than normal. The one parathyroid examined microscopically showed diffuse sclerosis. This case cannot be accepted as one of proved parathyroid insufficiency because no phosphorus studies were done. References to other French works on syphilis of the parathyroids may be found in this article.

Dieterich<sup>30</sup> reviews the subject of parathyroid lesions in acute infectious and comments on the scarcity of observed parathyroid lesions in the infectious diseases (scarlet fever, measles, diphtheria, typhoid, etc.). Garnier<sup>35</sup> found degenerative changes in two cases of scarlet fever. Bojew<sup>36</sup> in 1926 injected nine dogs with varying doses of diphtheria toxin. In some, spastic motions occurred two to 12 days later. Various changes were observed in the parathyroids, including vascular dilatation, effusion of blood, hydropic degeneration and necrosis of cells. The lesions were well illustrated; unfortunately there were no blood chemical studies.

Fibrosis of the parathyroids occasionally occurs, but is usually secondary to conditions such as syphilis, tuberculosis, or lymphoma. Haberfeld, however, found fibrosis (scarring) of two glands, round cell infiltration in a third, and atrophy in the fourth in a woman dying in pregnancy with tetany.

Amyloidosis<sup>18, 21</sup> and chronic passive congestion<sup>23, 21</sup> do not concern this discussion. Hydrops of the parathyroid glands in association with what was interpreted as mild inflammation has been reported.<sup>15</sup>

It is probably of little value to attempt to explain one disease of unknown etiology by comparing it with another. However, attention should be called to the disease entity in which all parathyroid tissue is tremendously hypertrophied and in which there is accompanying hyperparathyroidism.<sup>38, 39</sup> This disease must be due to some disorder. It is just possible that the disease under discussion is due to a disturbance at the same place in the opposite direction.

A survey of the 14 cases of idiopathic hypoparathyroidism cited above reveals surprisingly little of etiological significance. There was nothing in the histories to suggest an hereditary factor. There were nine males and five females. The ages of onset suggest that there are two groups, a childhood and adolescent group and an elderly group. The actual ages were 2½, 3, 3½, 4, 7, 8, 9, 12, and 14 and 38, 41, 43, 44, and 52. It should be

noted that there is a gap of 24 years between the age of 14 and that of 38. It is perfectly possible that the cause of the disease in the two groups will be found to be entirely different. The disease once established apparently remains permanently. In several of the cases the disease was precipitated by an acute infection. Thus the boy of 14 reported by Albright and Ellsworth had a tonsillectomy just prior to the onset of the tetany. The same was true of Cantarow's girl of seven. Kirklin and Childrey's patient developed tetany following measles and a complicating nephritis. Case 6 likewise developed tetany shortly after the measles. Case 2 was suffering from bilateral otitis media at the time of onset of her tetany, and case 5 developed tetany during an attack of "influenza." The above facts, coupled with the observations showing parathyroid degenerative changes in acute infections<sup>35, 23, 24</sup> suggest that bacterial or virus agents may be etiologically responsible for some cases of idiopathic hypoparathyroidism. However, it must be remembered that infections are apt to precipitate the symptoms of tetany in latent tetany.

#### SUMMARY AND CONCLUSIONS

The criteria necessary for a diagnosis of chronic idiopathic hypoparathyroidism are set forth. These should include low serum calcium and high serum inorganic phosphorus levels, normal bone texture by roentgenogram, and the absence of renal insufficiency.

Eight cases of the disease collected from the literature are cited and six new cases are added.

The autopsy findings are given in one fatal case. The parathyroid glands were normal in size but histologically all the epithelial cells were entirely replaced by fat cells, a finding heretofore not recorded in parathyroid pathology. No other clinically proved case with an autopsy was found in the medical literature.

A survey is made of the pathological lesions previously reported which could conceivably interfere with parathyroid function.

The possibility is mentioned that idiopathic hypoparathyroidism may be the antithesis as regards the parathyroid disorder of idiopathic hypertrophy of the parathyroids with hyperparathyroidism.

Attention is called to the fact that the disease usually starts in childhood or adolescence and, if not then, not until about forty. In several instances the onset was closely related to acute infections. The possibility of some bacterial or virus infection injuring the glands is discussed.

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# ESSENTIAL HYPERTENSION AND CHRONIC HYPERTENSIVE ENCEPHALOPATHY

## (A Clinico-Pathologic Study) \*

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THE associated renal and cardiac lesions of essential hypertension are well known; the neural complications, however, are less well established. The question frequently arises whether the neurological symptoms are caused by cerebral hemorrhages as a result of rupture of diseased vessels, encephalomalacias from thrombosis of the larger atherosclerotic cerebral vessels or encephalopathic changes secondary to implication of the cerebral arterioles. Our cases showed arteriolar involvement and clinical symptoms characterized by headaches, dysesthesias, fleeting paralysis, personality changes, intellectual impairment and a prolonged progressive course. The term "chronic hypertensive encephalopathy" is most appropriate for this group because of the diffuse areas of demyelination, focal hemorrhages and areas of devastation. In a series of seven cases of essential hypertension, all showed such changes. This condition should not be confused with "hypertensive encephalopathy" described by Fishberg,<sup>1</sup> characterized by sudden cerebral vasoconstriction associated with acute episodes of sudden marked elevations of blood pressure, severe headaches and convulsions. A reevaluation and reinterpretation of this subject in the light of the pathologic changes reported in the literature and those shown in our cases are of importance.

### CASE REPORTS

*Case 1.* B. L., a man, aged 35, was admitted to the Montefiore Hospital on January 3, 1929. For four years (1916 to 1920), the patient suffered from attacks of nausea, numbness, inability to speak, stiffening of the mouth and coldness of the extremities. These episodes would last 15 to 20 minutes, were not associated with loss of consciousness and were followed by generalized weakness lasting for one to two days. The patient was well from 1920 to 1925. In April 1925 there developed weakness of the right side of the face and right arm, aphasia and difficulty in swallowing. Examination at that time revealed hypertension. After three months progressive mental deterioration was noted but the aphasia cleared up partially.

*Physical Examination:* Examination revealed enlargement of the heart to the left and gangrene of the toe. The blood pressure was 190 systolic and 130 diastolic.

*Neurological Examination:* The patient was unable to walk. There were bilateral hyperreflexia, Babinski toe signs, ankle clonus and absent abdominal reflexes. Partial aphasia and questionable apraxia and agraphia were present. The speech was dysarthric. The sensory examination was unreliable. The optic fundi showed moderate arterial spasm. There was a left homonymous hemianopsia. The pupils were unequal and irregular; the left did not react to light and the reaction of the right

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was sluggish. There was a right supranuclear facial paresis. The patient was inattentive, irritable, uncoöperative and showed marked intellectual deterioration.

*Laboratory:* The maximum specific gravity of the urine was 1.019. Hemoglobin 80 per cent. The urea nitrogen was 23.6 mg. per cent on admission but rose to 72 mg. per cent just before death. The blood Wassermann reaction was negative.

*Course:* The blood pressure varied greatly, at times dropping to 120 systolic, 80 diastolic with subsequent rises to its previous level. At one time it reached 210 systolic, 140 diastolic. On May 11, 1929, the patient had a clonic convulsion lasting 10 minutes and involving the right upper and lower extremities. Several days later bronchopneumonia set in and he died on May 16.

*Anatomic Diagnosis:* Cerebral arteriosclerosis, arterioplasmic sclerosis of the kidneys with subacute malignant changes; cardiac hypertrophy; hemorrhagic bronchopneumonia; fibrinopurulent pericarditis.

*Autopsy of the Nervous System:* The brain was edematous. Horizontal sections disclosed areas of softening in the right temporal and occipital convolutions and of the left third frontal, pre- and postcentral convolutions and the internal capsule (figure 1). Small areas of destruction were present throughout the centrum ovale of both hemispheres.

*Microscopic Examination:* Examination of the involved cortical convolutions stained by the cresyl violet method revealed circumscribed areas of destruction (figure 2 A), distortion in the arrangement of the cyto-architectural layers (figure 2 B), almost complete loss of ganglion cells and endothelial proliferation of capillaries (figure 2 C). Small areas of devastation surrounded the smaller arterioles. The ganglion cells in these areas showed all types of pathologic changes, such as sclerosis, calcification, ischemia, chromatolysis and complete destruction. The white matter contained small areas of softening filled with compound granular corpuscles, scattered areas of devastation, collections of glia cells and glia nodules. The larger vessels showed arteriosclerosis with intimal proliferation. The precapillary arterioles revealed narrow lumina, marked hypertrophy of the media with an increase in the number of nuclei. Hyalin changes in the media were also present.

*Comment:* The onset of the symptoms 13 years before death, the predominance of the cerebral symptoms throughout the course of the illness, the presence of diffuse cerebral lesions and the changes in the precapillary arterioles were the outstanding features. There was some evidence of renal involvement as indicated by the limitation in the concentrating power of the kidney. The terminal rise in blood urea was probably the result of the severe bronchopneumonia.

*Case 2.* B. N., a woman, aged 38, was admitted to this hospital on June 3, 1931, complaining of severe headaches and occasional attacks of dizziness. She suffered from diabetes and hypertension for several years. In August 1931 a right-sided hemiplegia developed; this cleared up partially. On June 20, 1931, the patient experienced a sensation of "something falling on the left side of her head." A few hours later blindness, which lasted a few days, appeared. Vision improved gradually, but never completely.

*Physical Examination:* Examination on admission revealed an enlarged heart and a blood pressure of 275 systolic and 170 diastolic. Fundus examination showed copper wire tortuous arteries with retinal hemorrhages in the left eye.

*Neurological Examination:* Examination disclosed a slight right-sided weakness with hyperreflexia, a questionable Babinski sign, diminished right abdominal reflex and a slight right facial weakness. The left pupil was larger than the right and both reacted sluggishly to light.



*Laboratory Data:* The maximum specific gravity of the urine was 1.021. Albumin was present in amounts varying from a trace to two plus. The glucose in the urine was negative. Glucose tolerance test gave a diabetic curve with a peak of



FIG. 1. (Case 1.) Area of destruction of the right motor region and the Island of Reil. Notice numerous areas of destruction throughout the white matter.

347 mg. per cent two hours after the administration of the glucose. Urea nitrogen was 17.1 mg. per cent. The Wassermann reaction of the blood was negative.

*Course:* On June 22, 1931, there developed a left-sided convulsion followed by a left hemiplegia, unconsciousness, projectile vomiting and cyanosis. Examination at

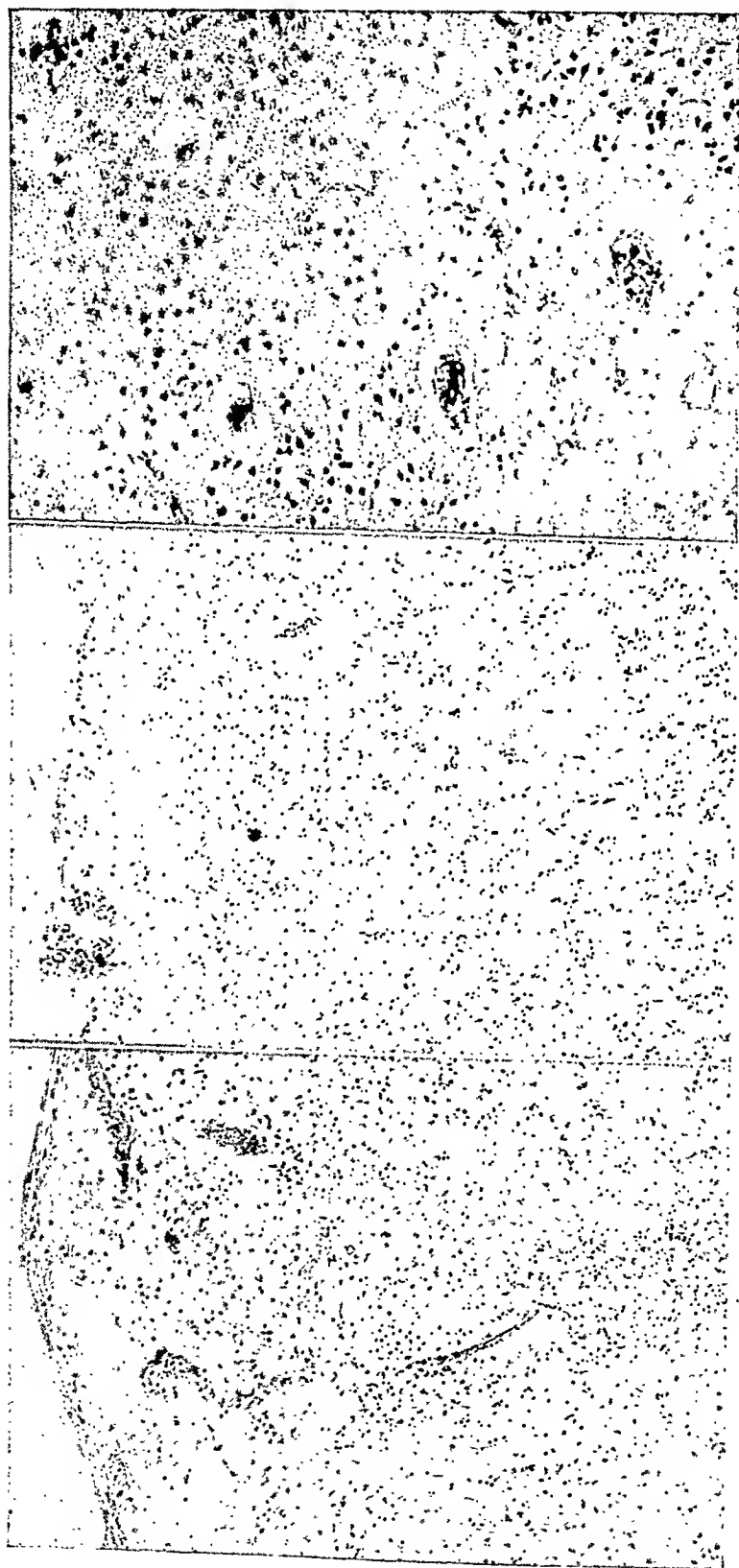


FIG. 2 A.

FIG. 2 B.

FIG. 2 C.

FIG. 2 A. (Case 1.) *Left.* Small area of softening with destruction in the arrangement of the cyto-architectural layers. Cresyl violet  $\times 50$ .  
 FIG. 2 B. (Case 1.) *Center.* Distortion in the arrangement of the cyto-architectural layers with dropping-out of nerve cells. Cresyl violet  $\times 50$ .  
 FIG. 2 C. (Case 1.) *Right.* Area of devastation with endothelial proliferation of the cortical vessels. Cresyl violet  $\times 100$ .

that time revealed generalized flaccidity with hyperreflexia, absent abdominal reflexes and bilaterally positive Babinski signs. A lumbar puncture revealed bloody fluid. Patient died shortly afterward.

*Anatomic Diagnosis:* Cerebral arteriosclerosis; thrombosis of branches of the middle cerebral artery; rupture of pontine branches; coronary sclerosis; hypertrophy and dilatation of the heart; arteriosclerosis of the kidneys.

*Autopsy of the Nervous System:* There was marked atherosclerosis of the vessels at the base of the brain. A subarachnoid hemorrhage was present over the temporal lobes, the peduncles and the cerebellum. An area of softening was noted in the left caudate nucleus and pulvinar. A fresh pontine hemorrhage extended caudally into the medulla oblongata and cerebellum.

*Microscopic Examination:* In the myelin sheath preparations, numerous small areas of softening involved the left corona radiata near the corpus callosum, the internal capsule, and the medial and lateral thalamic nuclei (figure 3 A). The right caudate and thalamus were the seat of small areas of cystic degeneration. In the sections stained by the cresyl violet method, some of these areas had a honey-combed appearance (figure 3 B), were filled with compound granular corpuscles, proliferating vessels and slight fibroblastic reaction. The small arterioles were thickened and showed beginning hyalinization of their walls; there was diminution in the size of the lumen. Sections of the pons disclosed a massive hemorrhage destroying most of the pontine fibers, the medial lemniscus, the thalamo-olivary and rubro-spinal tracts and the trapezoid body. The fourth ventricle was filled with blood. A section of the cerebellum stained by the cresyl violet method revealed a glia nodule in the white matter of the left hemisphere.

*Comment:* The headaches and dizziness from which the patient suffered for several years before her death, were undoubtedly secondary to disturbances in the cerebral circulation as expressed in the form of focal areas of softening. The temporary hemiparesis and visual complaints were also caused by the advanced arteriolar disease. The pontine hemorrhage was the cause of the death. The course of this patient's hypertension was characterized essentially by symptoms of progressive cerebral involvement.

*Case 3.* J. T., a man, aged 28, was admitted to this hospital on February 25, 1932, with a history of dizzy spells since 1930. Later the patient complained of malaise, occasional nausea and vomiting and diplopia. A diagnosis of malignant hypertension was made. On January 1, 1932, there developed a right hemiplegia and marked emotional lability.

*Physical Examination:* Examination revealed peripheral arteriosclerosis, an enlarged heart, bilateral papilledema with thickening of the arterioles, and a blood pressure of 180 systolic and 130 diastolic.

*Neurological Examination:* Examination disclosed pathological laughter and crying; right spastic hemiplegia with pyramidal tract signs; spastic left lower extremity with a positive Babinski toe sign; irregular pupils, the left larger than the right, both reacting sluggishly to light; bilateral weakness of the muscles supplied by the fifth nerve; complete paralysis of the right seventh nerve; paralysis of the palate; incomplete protrusion of the tongue, evidence of bilateral involvement of the eleventh nerve and urinary and fecal incontinence.

*Laboratory Data:* The urine concentrating power was good. The presence of albumin was detected once. Hemoglobin 85 per cent. The blood urea nitrogen was normal. The Wassermann reactions of the blood and spinal fluid were negative.

*Course:* The patient developed bronchopneumonia and died on October 4, 1932.

*Anatomic Diagnosis:* Generalized arteriosclerosis; arteriolosclerosis of the brain,



FIG. 3 A.

FIG. 3 A. (Case 2.) *Left.* Small areas of softening involving the corpus callosum, internal capsule, and the medial and lateral thalamic nuclei.  
FIG. 3 B. (Case 2.) *Right.* Honey-combed appearance. Cresyl violet  $\times 100$ .



FIG. 3 B.

kidney, spleen, heart, pancreas, testicles and psoas muscle; hypertrophy of the heart; bilateral lobar pneumonia.

*Autopsy of the Nervous System:* Examination of the brain revealed marked atherosclerosis of the vessels of the circle of Willis. A large area of softening destroyed the inferior portion of the left internal capsule and parts of the caudate and putamen. Another area of softening on the right involved the external seg-



FIG. 4. (Case 3.) Medium sized arteriole showing marked endarteritic changes with obliteration of the lumen. Resorcin-fuchsin  $\times 50$ .

ment of the globus pallidus, putamen, internal capsule and pulvinar. Punctate hemorrhages were found in the tip of the right caudate and medulla oblongata.

*Microscopic Examination:* In the myelin sheath preparation, in addition to the large areas of softening, there were also numerous small areas of demyelination. The cerebral vessels showed marked proliferation of the intima and splitting of the internal elastic lamina. The medium-sized arterioles and capillaries showed marked endarteritic thickening, with practically complete obliteration of the lumen (figure 4).

*Comment:* This case is of interest because of the similarity in the alterations of the arterioles throughout all organs. The main clinical signs and pathologic changes were those referable to the central nervous system.

*Case 4.* S. L., a man, aged 38, was admitted to this hospital on November 2, 1935, with a history of hypertension of three years; headaches and nocturnal dyspnea of one year, increasing pallor and loss of weight of six months' duration and difficulty in speech and weakness of the right side of the body one day prior to admission.

*Physical and Neurological Examination:* The patient was somnolent and pale. The heart was enlarged. The blood pressure was 250 systolic and 170 diastolic. Marked peripheral and retinal sclerosis with hemorrhages and exudates was noted. The right pupil was larger than the left. There was a flaccid right hemiplegia and motor aphasia.

*Laboratory Data:* The urine showed a specific gravity of 1.018, 4 plus albumin, and numerous casts with occasional red blood cells and white blood cells. The Wassermann reaction of the blood was negative. The spinal fluid pressure was 260 mm. of water. The blood urea nitrogen was 37.2 mg. per cent and it rose terminally to 55 mg. per cent.

*Course:* On November 26, 1935, the patient became drowsy and developed a global aphasia. Two days later he had a convulsion and died.

*Anatomic Diagnosis:* Generalized arteriosclerosis with involvement of brain, kidney and coronary vessels; rupture of branches of the left middle cerebral and basilar arteries; cardiac hypertrophy and dilatation.

*Autopsy of the Nervous System:* The vessels at the base of the brain showed marked atheromatous plaques. There was a hemorrhage in the region of the left insula and basal ganglia. Hemorrhages were present in the pons, destroying the greatest part of the tegmentum and in the medulla oblongata.

*Microscopic Examination:* In the myelin sheath preparation, the left centrum ovale stained poorly. The large hemorrhage destroyed the left insula, internal capsule and basal ganglia. The involved convolutions revealed a loss in the arrangement of the cyto-architectural layers. Ring hemorrhages were found in areas adjacent to the massive hemorrhage. The ganglion cells showed various pathologic changes; the ischemic cell changes were the most prominent. Smaller areas of demyelination in other regions with relative acellularity and an occasional glia nodule were seen. The capillary walls throughout the nervous system were thickened while the small arterioles showed early hyalin degeneration of the media with an increase in the thickness of its wall and narrowing of its lumen. The perivascular spaces appeared dilated in many areas; the adjacent brain tissue was edematous. Perivascular gliosis was also present.

*Comment:* This case illustrates the simultaneous involvement of kidney, heart and brain with death from cerebral lesions. Although the neurologic signs indicated involvement of the left middle cerebral artery, lesions were found throughout the central nervous system.

*Case 5.* I. W., a woman, aged 40, was admitted to this hospital on August 25, 1932, with a history of severe frontal headache and hypertension for eight years. During the last four years, the patient had attacks of numbness on the left side of the body, associated with blurring of vision. In January 1932, she complained of severe abdominal pain and vomiting and lost 30 to 40 pounds in weight in one month.

*Physical and Neurological Examination:* The patient was emaciated. The peripheral vessels were moderately sclerotic; the heart was enlarged. The blood pressure was 190 systolic and 120 diastolic. The fundi showed bilateral papilledema, more marked on the right, thickened retinal arteries, and numerous exudates and flame-

shaped hemorrhages. There was a slight left hemiparesis with a positive Babinski toe sign on that side and a normal plantar response on the right.

*Laboratory Data:* Examination of the urine disclosed a specific gravity of 1.018, 4 plus albumin, numerous casts with a few white blood cells and occasional red blood cells. The hemoglobin was 54 per cent. There were 2,500,000 red blood cells. The blood urea on admission was 23 mg. per cent.

*Course:* On September 3, 1932, the patient vomited and complained of severe frontal headache. The blood pressure at that time had risen to 270 systolic and 160 diastolic. She became drowsy and later semi-stuporous. Examination at this time revealed a left homonymous hemianopsia, hypesthesia on the left side of the body, slight neck rigidity and a suggestive Brudzinski sign on the right. Lumbar puncture yielded clear fluid under a pressure of 240 mm. of water. The stupor continued, the paresis became more marked, the spasticity was replaced by flaccidity and the neck rigidity increased. A second lumbar puncture yielded xanthochromic fluid. The blood chemistry at this time was normal. The blood urea nitrogen rose to 54 mg. per cent, and the patient died on the following day.

*Anatomic Diagnosis:* Generalized arteriosclerosis including the nervous system, kidney and heart; hypertrophy and dilatation of the heart; bronchopneumonia; cholelithiasis.

*Autopsy of the Nervous System:* There were two large hemorrhages in the right temporal lobe; these extended into the parietal and occipital regions (figure 5 A). Other small areas of destruction were found throughout.

*Microscopic Examination:* An extensive area of devastation of both white and gray matter, punctate hemorrhages and pronounced proliferation of small arterioles and capillaries were noted in the right island of Reil. Adjacent areas showed moderate dropping out of nerve cells, ischemic cell changes, a similar but less marked proliferation of the vessels and perivascular gliosis. The small arterioles were thickened and showed extensive hyalinization, hyperplasia of the endothelium, narrowing of the lumen and adventitial proliferation (figures 5 B and C). Reduplication of the elastic lamina of the small thickened vessels was clearly brought out in the resorcin-fuchsin preparation. The adventitial spaces contained compound granular corpuscles. Similar but less marked changes were also noted in the frontal, parietal and occipital convolutions.

*Comment:* The cerebral changes in this, as in the other instances, were diffuse. The patient had suffered from headaches for eight years. For four years she had experienced attacks of numbness and blurring of vision. The abdominal pain and vomiting may have been cerebral in origin or may have been caused by the cholecystitis and cholelithiasis. The cerebral hemorrhage was a terminal event.

*Case 6.* F. L., a woman, aged 42, was admitted to this hospital on March 25, 1930, complaining of severe frontal headaches, dizziness, occasional attacks of epistaxis, easy fatigue, dyspnea on exertion and palpitation of the heart for the past four years. In January 1930, on awakening, she found her left side paralyzed.

*Physical Examination:* Examination revealed a large heart, an enlarged liver, some fluid at the base of the right pleural cavity and a blood pressure of 240 systolic and 140 diastolic. There was a residual hemiplegia on the left side.

*Laboratory Data:* The blood urea nitrogen was 14.9 mg. per cent. The urine contained 2 plus albumin and the specific gravity was 1.016.

*Course:* On the day after admission, the patient suddenly became comatose and showed signs of paralysis of the right side of the body. She remained in coma and died the next day.

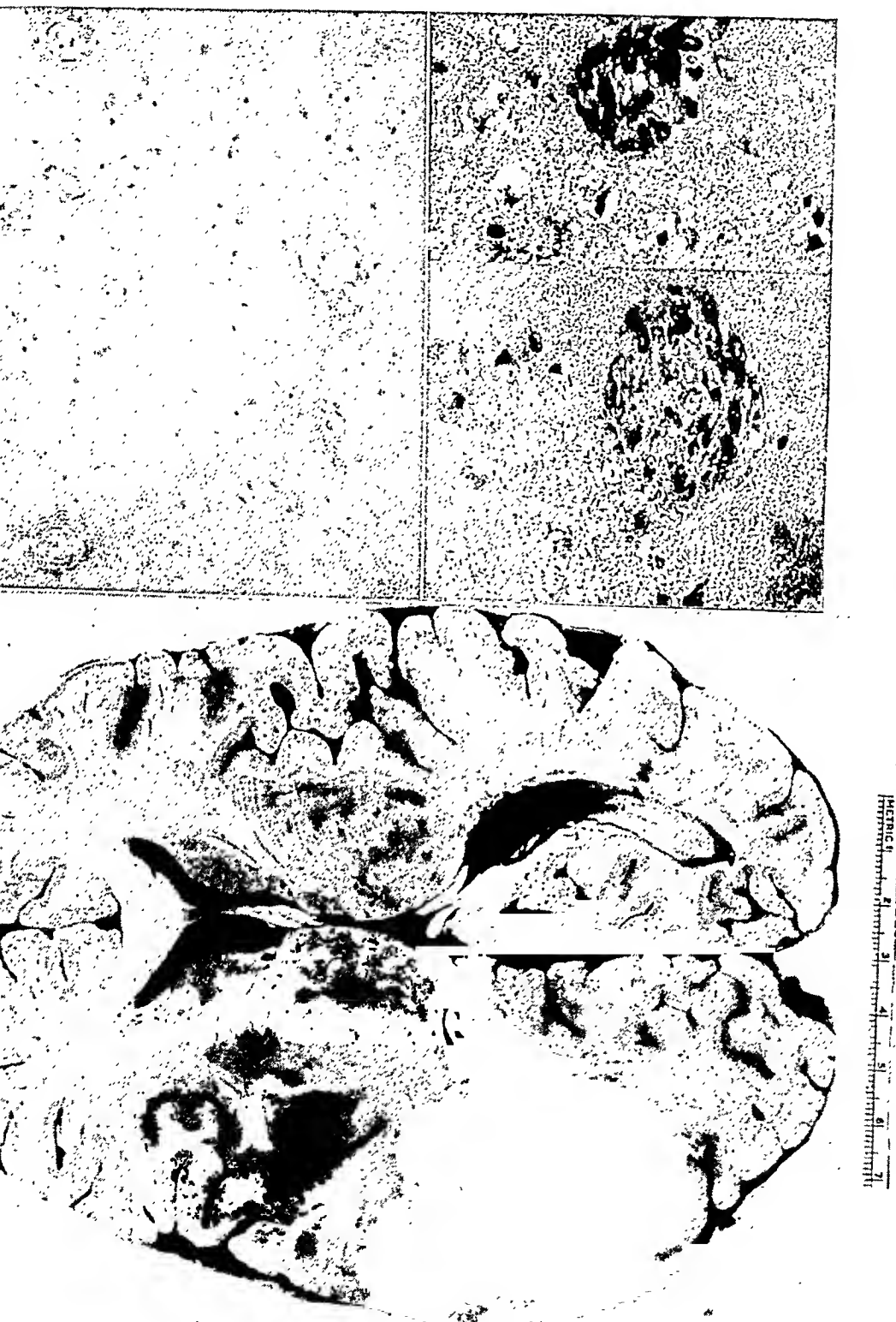


FIG. 5 A. (Case 5.) *Left.* Extensive hemorrhage in the right temporal and inferior parietal convolutions and numerous areas of destruction throughout.  
 FIG. 5 B. (Case 5.) *Upper right.* Hyalinization and endothelial proliferation of the small vessels with narrowing of the lumen. Cresyl violet  $\times 100$ .  
 FIG. 5 C. (Case 5.) *Lower right.* Proliferation of the adventitia of the cortical vessels. Hematoxylin-eosin  $\times 200$ .



*Anatomic Diagnosis:* Generalized arteriosclerosis including the nervous system, kidney and heart; cardiac hypertrophy and dilatation.

*Autopsy of the Nervous System:* The vessels at the base of the brain were markedly sclerotic. There were two hemorrhages in both hemispheres involving the internal capsules. The hemorrhage on the left was smaller than on the right, was more recent in origin, and extended into the parietal lobe. The hemorrhage on the right was organized.

*Microscopic Examination:* Sections from various cortical regions showed small areas of devastation and thickening of the walls of the small arterioles with narrowing of their lumina. In the resorcin-fuchsin preparation, the muscularis of the small arterioles showed the greatest hypertrophy. There was reduplication of the elastic lamina. The perivascular spaces were moderately dilated. A moderate loss of nerve cells in the cortical tissue, glia cells and axis cylinders in the white matter was noted around these sclerotic vessels. The normal arrangement of the cyto-architectural layers was lost.

*Comment:* In this instance the associated renal, cardiac and cerebral involvement was evident. In addition to the cerebral hemorrhages there were other diffuse lesions in the nervous system directly due to deficient circulation as a result of the changes in the walls of the arterioles and capillaries.

*Case 7.* R. G., a woman, aged 50, was admitted to this hospital on March 22, 1932. In 1928 the patient sustained a minor injury to her left hand which was immediately followed by a generalized convulsion lasting five minutes and unconsciousness. Soon there developed paralysis of the left side from which she recovered completely in six weeks. In December 1929, she became dizzy and fell, striking the back of her head. Two weeks later, occipital headache and nausea and stupor for about 2½ days set in. Upon regaining consciousness she was irrational and showed impairment of memory and judgment. The blood pressure at that time varied between 190–210 systolic and 110–140 diastolic. The left disc margin was blurred. In 1930 following some excitement, she had loss of memory for several weeks. On February 21, 1932, upon awakening, she experienced a weakness of the left side of the body and diplopia.

*Physical Examination:* Examination revealed an enlarged heart, a blood pressure of 210 systolic and 150 diastolic, hyperemia of the left disc, edema of the retina and a few small hemorrhages in the right fundus.

*Neurological Examination:* Examination revealed a left flaccid hemiparesis with exaggerated deep reflexes and positive Hoffmann and Babinski signs; intention tremor in left upper and lower extremities with asynergia; myoclonic movements of the eyes, soft palate, perioral muscles, tongue and lower jaw; a constant horizontal and rotary nystagmus; weakness of the right lateral rectus muscle, impairment of upward gaze and conjugate deviation to the left and a right supranuclear facial weakness.

*Laboratory Data:* The specific gravity of the urine varied between 1.012 and 1.016. A trace of albumin was present. The blood chemistry was normal and the Wassermann reaction of the blood was negative.

*Course:* Later the patient became mentally confused, had difficulty in swallowing, experienced choking sensations, urinary incontinence, emotional instability with outbursts of weeping and definite episodes of mental defect and disorientation. The neurological status was unchanged except for the addition of a right hemiplegia with positive signs of pyramidal tract involvement, dysarthria, pseudo-bulbar speech, impaired pain and temperature sensibility on the left side and a poor response of the left pupil to light. On December 8, 1932, she became unconscious, developed a flaccid paralysis of all extremities, signs of pneumonia and she died on December 13.

*Anatomic Diagnosis:* Generalized arteriosclerosis involving brain, kidney and heart; hypertrophy and dilatation of the heart; lobar pneumonia (right).

*Autopsy of the Nervous System:* The vessels at the base showed marked arteriosclerosis. There were areas of softening involving the first and second right orbital convolutions, the right caudate, the right centrum ovale, the right external nucleus of the thalamus (figure 6 A) and the pons near the right sixth nerve nucleus. Small foci of softening were found throughout the central nervous system. There was a fresh hemorrhage involving the left caudate, thalamus and internal capsule (figure 6 B).

*Microscopic Examination:* The vessels showed arteriosclerotic and endarteritic changes. In sections through the aqueduct, there were numerous thickened hyalinized vessels with little involvement of surrounding neural tissue. The small arterioles in the pons showed marked thickening of the intima and a pronounced glial reaction about them (figure 6 C). Numerous glia nodules were noted throughout, especially in the white matter of the cerebellum. The nerve cells of the various involved areas showed all types of pathologic changes.

*Comment:* The neurologic symptoms and signs are amply accounted for by the diffuse cerebrovascular disease. The brain in this case obviously bore the brunt of the changes secondary to hypertensive arteriolar disease.

## DISCUSSION

The original concept that the so-called Bright's disease associated with hypertension was essentially a disease of the kidneys was first questioned by Gull and Sutton<sup>2</sup> in 1872, who showed that arteriolosclerosis was not confined to the arterioles of the kidneys. Through the investigations of Jores,<sup>3</sup> Munzer,<sup>4</sup> Evans<sup>5</sup> and others, this fact was partially confirmed. Fishberg<sup>6</sup> in 1925 studied the anatomic findings in essential hypertension and reported that, although the kidney is most involved, other organs were also affected. The cerebral arterioles, he found, were diseased in 19 per cent of the cases. Branch and Linder<sup>7</sup> in 1926, Keith, Wagener and Kernohan<sup>8</sup> in 1928 and Kernohan, Anderson and Keith<sup>9</sup> in 1929 emphasized the diffuse disturbance in the arterial tree caused by hypertension.

The work of Volhard and Fahr,<sup>10</sup> Fahr,<sup>11</sup> Janeway,<sup>12</sup> Allbutt,<sup>13</sup> Ellis and Marrack,<sup>14</sup> and more recently of Wagener and Keith,<sup>15</sup> Fishberg,<sup>16</sup> Keith, Wagener and Kernohan,<sup>8</sup> and others, has led to a better understanding of the clinical course and associated pathology of cases of hypertension. It is now recognized that they generally terminate in one of three ways: (1) most commonly from cardiac failure, coronary sclerosis frequently complicated by slow or acute occlusion; (2) cerebral accident; and (3) least commonly, from renal insufficiency (10 per cent or less).

Although the clinical course of each type varies considerably, the pathologic changes are essentially quite similar. The secondary degenerative changes in the heart and kidney which give rise to well recognized clinical syndromes, also may take place in the brain causing a condition which has been called "cerebral vascular disease," "arteriosclerotic brain atrophy (Alzheimer)," "encephalomalacia" or "cerebral arteriosclerosis."



FIG. 6 A.

FIG. 6 B.

FIG. 6 C.

FIG. 6 B.

FIG. 6 C.

*Left.* Small areas of softening in the right lateral thalamic nucleus and internal capsule.  
*Center.* Hemorrhage in the left thalamus.  
*Right.* Thickening of vessel and perivascular gliosis. Cresyl violet  $\times 100$ .

Many of the clinical symptoms such as headaches, dizziness, dysesthesias, fleeting paralyses, transient aphasia, temporary or permanent personality changes and intellectual impairment are explained on the basis of the findings described in our cases.

An attempt was made to demonstrate that cerebral changes are a frequent accompaniment of cardiac and renal disease, during the course of essential hypertension. In our cases the brain was more extensively involved than the other organs. The diffuse areas of softening, the focal hemorrhages, the small focal areas of devastation, the disturbances in cyto-architectural arrangement, the dropping-out of ganglion cells, the degenerative nerve cell changes and the glia nodule formation were due to arteriolar changes. These are the indisputable marks of long-standing progressive lesions, many of which have their clinical counterparts, those in silent areas having none. The more obvious hemorrhages and thromboses of larger vessels are all secondary to the disease of the arteries produced by elevated blood pressure.

Clinically, the significant facts in this series showed that all the patients were comparatively young individuals, the average age being 38. Several cases in older persons were deliberately excluded to eliminate the complicating factors of senile arteriosclerotic encephalopathy. The average span of life following the onset of the symptoms was about five years. The first case lived the longest—13 years, and the fourth case lived for only 1½ years. Five out of the seven cases died of a terminal cerebral hemorrhage. The average systolic blood pressure was 210 and the average diastolic was 140. The patient who lived the longest had the lowest blood pressure.

The cases were all characterized clinically by a succession of neurological symptoms due to large and small cerebral vascular insults. Cardiac and renal symptoms were relatively inconspicuous and unimportant. The course was progressive; cerebral manifestations occurred before there was any clinical or laboratory evidence of renal or cardiac insufficiency. Death in most instances was ultimately the result of "cerebral failure."

Keith, Wagener and Kernohan<sup>8</sup> described a cerebral form of malignant hypertension, a characteristic feature of which was edema of the disc, often out of proportion to the other retinal changes. This condition which was present in all their cases was found in only three of our cases. None of the three cases ran a course radically different from the others or showed pathologic changes that would distinguish them from the remainder of the group. The pathologic changes in four brains they examined were similar to those found in our cases. Although Keith's classification appears to be legitimate, we believe that a regrouping is warranted, based not upon the presence or absence of a certain type of retinitis, but upon striking clinical and pathologic resemblances. In the absence of necrotizing arteriolitis and renal insufficiency, the diagnosis of "malignant phase of essential hypertension," as reported by Fishberg,<sup>16</sup> and Klemperer and Otani,<sup>17</sup> cannot be applied to our cases.

The histopathologic changes previously described by Bodechtel<sup>18</sup> and Hechst<sup>19</sup> in uremia are similar to those observed in our cases and most likely were due to accompanying hypertensive vascular disease. Bodechtel<sup>18</sup> demonstrated small areas of devastation in the cortex, glia nodule formation and small areas of softening in uremia. Hechst<sup>19</sup> noted in cases of uremia hyalin degeneration of the media of the small vessels of the brain, areas of softening, chronic cell changes and glia nodules. Neubürger,<sup>20</sup> who described diffuse neural changes, mentioned the difficulty in differentiating between hypertensive, arteriosclerotic and embolic lesions. He believed, however, that the presence of red infarcts, severe arteriolar damage and the ischemic cell changes in Ammon's horn are characteristic of hypertensive involvement.

"Chronic hypertensive encephalopathy" is the appropriate term for cases with progressive and diffuse cerebral changes and focal signs caused by arteriolar disease, secondary to hypertension.

#### SUMMARY AND CONCLUSIONS

1. Hypertension is associated with generalized arteriolar changes.
2. In some instances, the cerebral vessels are primarily affected, resulting in widespread neural involvement, with relative sparing of the heart and kidney.
3. Clinically these cases were characterized by diffuse neurological signs and symptoms and by a progressive down-hill course. Death resulted from cerebral failure, usually from a terminal hemorrhage.
4. The term "chronic hypertensive encephalopathy" is proposed to describe these cases.

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# HEMOLYTIC JAUNDICE AND MACROCYTIC HEMOLYTIC ANEMIA: CERTAIN OBSERVATIONS IN A SERIES OF 35 CASES \*

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DURING the past six years opportunity has been afforded to study 35 patients † exhibiting evidence of hemolytic anemia or jaundice. These cases were divided as follows:

1. Microcytic (familial or congenital) type ..... 20
2. Macrocytic (secondary or acquired) type ..... 15
  - a. With liver disease ..... 8
  - b. With Hodgkin's disease ..... 3
  - c. With leukemia ..... 2
  - d. With chronic bleeding into ovarian cyst 1
  - e. With hyperthyroidism ..... 1

It will be noted that the cases in the second group were in all instances associated with other disease. The existence of a primary form of acquired hemolytic jaundice has been questioned more and more in recent years. There is little doubt that the vast majority, if not all of the cases of primary hemolytic jaundice are of the familial or congenital type. In the earlier literature (Eppinger<sup>1</sup>), patients whose jaundice appeared first in adult life, and in whose family no other members were icteric, were often wrongly classified as instances of the acquired type. This was true even though fragile microcytes were demonstrated. One of the cases of familial hemolytic jaundice in the present series illustrates how easily such a mistake might be made. This patient, a male 22 years of age, had first become jaundiced at 19. Since then there had been varying degrees of jaundice and anemia. The spleen was markedly enlarged. Deeply staining microcytes were numerous in the stained smear of his blood. In hypotonic saline hemolysis of the erythrocytes began at 0.68 per cent and was complete at 0.42 per cent. (Control: H<sub>1</sub> 0.44 per cent, H<sub>2</sub> 0.34 per cent.) Careful questioning of the

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† In somewhat more than a year since this paper was written, 13 additional instances of hemolytic anemia have been studied. Seven of these were typical cases of the familial, microcytic type, four were in association with leukemia, one was noted in a patient with cirrhosis of the liver, and another in a case of probable diffuse splenic fibrosis, or Banti's disease. The feces urobilinogen and reticulocyte percentage were elevated in varying degree in all of these cases. Of the four cases of leukemia, the anemia was macrocytic in three, as judged by mean corpuscular volume and mean diameter of the erythrocytes. Measurements were not recorded in the fourth. It is of interest that two of these four cases were instances of subleukemic, splenic reticuloendotheliosis. Outspoken macrocytosis was present in the two patients with cirrhosis, and with Banti's disease.

relatives failed to elicit a history of jaundice or splenic enlargement in any. The mother, father and six brothers were examined and none were found to exhibit jaundice or splenomegaly. Two of the members of the immediate family were examined as to fragility of erythrocytes. The resistance of one of the brother's erythrocytes to hypotonic saline was definitely diminished:  $H_1$  0.56 per cent,  $H_2$  0.42 per cent. The values for the father were normal:  $H_1$  0.44 per cent,  $H_2$  0.32 per cent. From this it is evident that the underlying affection was familial, although only the patient presented obvious manifestations, and these failed to appear until early adult life.

In two of the cases of macrocytic type, the hemolytic anemia persisted after removal of the associated pathologic conditions, which in one was a bleeding ovarian cyst, and in the other a diffuse hyperplasia of the thyroid with hyperthyroidism. Some of the features in the first of these two cases have already been described,<sup>2, 30</sup> but inasmuch as this is perhaps the most important case of the series, a more detailed report will now be given.

#### CASE REPORT

The patient was a female, 19 years of age. She had always been healthy until the age of 17 when she first noticed mild jaundice. This had frequently recurred, ushered in by slight chilly sensations and headache, and accompanied later by a dull diffuse abdominal distress. There was no familial history of jaundice. Examination revealed mild jaundice and obvious anemia. The spleen was not palpable, either at the time of the first, or of many subsequent examinations. A mass was palpable in the left lower quadrant of the abdomen; on bimanual examination, this was evidently in the region of the left ovary; the mass was smooth, firm and appeared to be cystic. Examination of the blood revealed: Hemoglobin 32 per cent, erythrocytes 1,150,000, leukocytes 6900, 76 per cent neutrophils. Stained smears exhibited marked anisocytosis of the erythrocytes with predominance of macrocytes; the average cell diameter was 8.8 micra. (This value was obtained with the Bock apparatus,<sup>4</sup> the normal for which in this vicinity is 7.6 to 8.0 micra.) The reticulocytes were 15 per cent. The resistance of erythrocytes to hypotonic saline was:  $H_1$  0.38 per cent,  $H_2$  0.32 per cent. (Control:  $H_1$  0.38 per cent,  $H_2$  0.30 per cent.) Marked spontaneous autohemagglutination was exhibited by the patient's blood. This was definitely related to temperature, the agglutination appearing first about 30° C., disappearing when the blood was warmed to 37° C. The agglutinins resided in the plasma and could be removed completely by repeated subjection of the same sample of plasma to washed erythrocytes, either those of the patient, or of another group O individual. It was possible to group the patient's blood only after dilution of at least 1:20 in physiological saline. The question arose as to whether autohemagglutination had interfered with measurement of the resistance of the erythrocytes to hypotonic saline. This possibility was excluded by carrying out the fragility test at a temperature of 37° C. Even with this precaution, no deviation from the normal was found. The icterus index at time of admission was 42; later, however, even with increasing anemia, it usually ranged from 12 to 20. The Van den Bergh reaction was positive and of the indirect type. The urine contained no bilirubin and but relatively small amounts of urobilinogen, varying from 2.4 to 9.8 mg. per day. The feces urobilinogen was markedly increased, ranging from 986 to 1106 mg. per day.

All of these findings indicated increased hemoglobin destruction, but since it was conceivable that internal bleeding might be responsible, an exploration of the abdomen with reference to the pelvic mass was decided upon. The patient was trans-



fused repeatedly and a large ovarian cyst containing 800 c.c. of dark brown fluid was removed from the left side of the pelvis. This fluid contained much hematin, but no bilirubin. The operation, however, failed to bring improvement; shortly afterwards the hemoglobin declined from 59 per cent, to which it had risen as a result of preoperative transfusions, to 39 per cent and then more gradually fell to a low of 23 per cent. Transfusions were again resorted to but were now often productive of severe febrile reactions and at times obviously initiated "hemolytic crises." The usual course of events was that an immediate rise of several points in hemoglobin level would occur, but within 24 hours the patient would experience increase in fever, nausea and jaundice, and the hemoglobin would rapidly decline. This was true following a direct transfusion as well as after citrated blood. The rather frequent untoward results of blood transfusions in hemolytic jaundice have been commented upon repeatedly in the recent literature.<sup>5, 6, 7, 8</sup> In two other cases of the present series blood transfusion was followed by a temporary increase in jaundice and a rather rapid decrease in hemoglobin. In the case just described the hemoglobin had declined to 28 per cent in spite of several transfusions. This was after an interval of 20 days subsequent to removal of the cyst. It was now decided to discontinue transfusions for a time in the hope that they might be tolerated better after a period of rest. During the next 10 days the hemoglobin declined further to 26 per cent; the reticulocytes were fluctuating between 10 and 17 per cent. At the end of this interval it was decided to transfuse the patient again and carry out splenectomy. Accordingly, transfusions of 500 c.c. of citrated blood were given, one each, on April 8, 9, and 11, 1935. Interestingly enough, these transfusions were attended by very little reaction. The hemoglobin had risen on April 11 to 51 per cent with 2,300,000 erythrocytes per cu. mm. Splenectomy was carried out by Dr. Owen Wangenstein. The spleen weighed but 440 gm.; microscopic study revealed marked congestion of the pulp, with rather narrow sinuses.

The immediate postoperative course was quite unlike that usually noted in cases of familial hemolytic jaundice. Instead of a progressive increase in hemoglobin and erythrocytes with a marked decline in urobilinogen excretion<sup>3c, 5</sup> the latter remained markedly elevated while the former steadily declined. This decline was associated with a marked drop in reticulocytes. All of these changes may be seen in the following table:

Date	Hemoglobin, Per cent	Erythrocytes, mill. per cu. mm.	Reticulocytes, Per cent
4-8-35.....			15.0
4-11.....	51	2.30	
Splenectomy			
4-15.....	51	2.70	0.3
4-16.....	48	2.21	0.6
4-17.....	49	2.38	1.8
4-18.....	46	2.28	3.6
4-19.....	46	2.20	4.8
4-20.....	40	2.07	8.6
4-22.....	48	2.63	22.2
4-24.....	49	2.59	216
4-26.....	54	2.66	16.8
4-29.....	57	3.02	12.2

From the above it will be seen that the anemia increased until the reticulocytes again became elevated. When these findings are compared with the urobilinogen excretion, it is evident that the patient suffered from another, although relatively mild, "hemolytic crisis," even after splenectomy. Fortunately, this was the last such episode. On April 25 the feces urobilinogen was found to be 1548 mg. per day, as con-

trasted with a normal range of 40 to 280 mg.<sup>3b</sup> By May 10, one month after splenectomy, the value had fallen to 429 mg. daily, still nearly twice the upper limit of normal; the icterus index at this time was 19. The very slow decline of the feces urobilinogen is quite dissimilar to the rapid decline usually observed following splenectomy in familial hemolytic jaundice.<sup>3c</sup> After May 15 the patient's condition improved steadily; by July 2 the icterus index had fallen to 10, and the feces urobilinogen to 203.6 mg. per day. On August 1 the hemoglobin had risen to 72 per cent and the erythrocytes to 3,180,000 per cu. mm. The patient was seen again at intervals, the last time in May, 1937. The hemoglobin was now 88 per cent, there was no icterus, and there had been no recurrence of symptoms. It is worthy of note that the autohemagglutination had now entirely disappeared although it persisted for several months after splenectomy.\*

The patient with hyperthyroidism and macrocytic hemolytic anemia was kept under observation for two months after subtotal thyroidectomy had been carried out. At this time the symptoms of hyperthyroidism had disappeared, the basal metabolic rate having declined from + 40 per cent prior to operation, to + 16 per cent. Nevertheless, the hemolytic anemia had persisted and the hemoglobin had fallen to 42 per cent. The feces urobilinogen remained constantly elevated, ranging from 500 to 1000 mg. per day. The patient returned to her home, refusing splenectomy. Several weeks later a report was received from her local physician that splenectomy had been carried out but that death, ascribed to pulmonary embolism, had occurred a number of days after operation.

Particular attention has been given to the first of these two cases because of its importance with reference to the question of acquired hemolytic jaundice. Regardless of the possibility that reabsorption of hematin from the hemorrhagic ovarian cyst may have stimulated blood destruction at the outset, it is quite clear that the condition of hemolytic anemia persisted to a dangerous degree long after removal of the cyst. The case must, therefore, be classified as an idiopathic one. As compared with familial hemolytic anemia, this case differed in three respects, which will now be considered in relation to the entire group of patients. These three respects are: (1) size of erythrocytes, (2) fragility of erythrocytes (resistance to hypotonic saline), (3) autohemagglutination. In the distinction of familial from acquired hemolytic anemia or jaundice, the first of these is unquestionably the most important.

#### SIZE OF ERYTHROCYTES

Of the 15 cases of acquired hemolytic anemia in the present series, all exhibited red blood cells at least slightly larger, and often much larger than the normal. Of the various diseases represented in this group, each has been previously noted to be associated at times with a macrocytic anemia. (Liver disease <sup>3c, 4, 9, 10</sup>; Hodgkin's disease and leukemia. <sup>3c, 11, 12</sup>) Of the 20

\* This patient was studied again on January 3, 1939. At this time the hemoglobin was 90 per cent, the erythrocytes 4,160,000 per cu. mm., the average diameter of the erythrocytes 7.8  $\mu$ , and the reticulocytes 2.2 per cent. There was no icterus and subjectively the patient was entirely normal.

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cases of familial hemolytic anemia or jaundice, represented in the present series, all exhibited red blood cells which were smaller, on the average, than normal. With the Bock erythrocytometer the average diameter was found to range from 6.6 to 7.2  $\mu$ , whereas in the acquired group it was regularly more than 8.0  $\mu$ . Evidence of familial incidence was obtained from the history or from examination of the relatives in each of the 20 instances of the familial type. With one exception, the history was negative in this respect in the macrocytic group. In one of the cases of cirrhosis of the liver, which will be referred to again in the following, the patient's brother was said to have died of "pernicious anemia."

#### RESISTANCE OF ERYTHROCYTES TO HYPOTONIC SALINE

Increased fragility of erythrocytes was not strictly limited to the microcytic (familial) group of cases. Two of the cases which were classified as macrocytic hemolytic anemia in association with liver disease, exhibited decreased resistance of the erythrocytes to hypotonic saline. In one of these, a female aged 30, hemolysis began at 0.64 per cent ( $H_1$ ) and was complete at 0.42 per cent ( $H_2$ ), whereas the control was:  $H_1$  0.52 per cent,  $H_2$  0.38 per cent. In the other, a female aged 68, the abnormality was less striking:  $H_1$  0.46 per cent,  $H_2$  0.40 per cent; control  $H_1$  0.40 per cent,  $H_2$  0.34 per cent. It should be emphasized that both of these patients were suffering from moderately severe anemia of macrocytic type; the average red blood cell diameter in the first was 8.35  $\mu$ , and in the second 8.1  $\mu$ . From this it is clear that increased fragility may at times occur in anemias other than those characterized by the presence of spherical microcytes. On the other hand, the present series of cases of familial hemolytic jaundice exhibited increased fragility without exception. In Gänsßlen's large series<sup>13</sup> a few exceptions were noted. Haden<sup>14a</sup> believes that the microcytes of familial hemolytic jaundice are more fragile because of their spherical shape; in the laking of normal erythrocytes by gradual addition of distilled water, he found that the normally biconcave discs first tend to become spherical and then undergo hemolysis as the solution becomes more hypotonic. This observation, coupled with the likelihood that the spherical microcyte is the chief inherited fault in the familial form of the disease, makes it difficult to conceive of cases which would not exhibit increased fragility. Conversely, one would not expect to observe increased fragility in macrocytic anemias, such as in the two which have just been mentioned. The question naturally arises as to whether the thickness of the macrocytes in these cases is increased to such a degree that increased fragility might be expected. Data from the second case yield some information in this regard:

Mean corpuscular volume: 133 cu. $\mu$	Normal 80-94 cu. $\mu$ (Wintrobe, 15)
Average diameter: 8.1 $\mu$	7.6-7.8 $\mu$
Cell thickness: $\frac{\text{vol}}{\pi r^2}$ (v. Boros. 16) = 2.6 $\mu$	1.2-2.0 $\mu$

From these findings it is evident that although the cells were slightly thicker than normal in proportion to their increased diameter, they were not spherical. At the time the above determinations were made the resistance of the erythrocytes to hypotonic saline was determined again, with the following result:  $H_1$  0.56 per cent,  $H_2$  0.42 per cent; control,  $H_1$  0.42 per cent,  $H_2$  0.34 per cent. (Further studies of this patient are described on page 1793.) This result is in accord with Vaughan's recent report<sup>14b</sup> that increased fragility invariably persisted after splenectomy but that spherocytosis disappeared in about 50 per cent of cases, a finding which indicates that some abnormality other than simple spherocytosis may be responsible for the increased fragility.

According to recent studies by Dameshek and Schwartz,<sup>29, 30</sup> the possibility would have to be considered that macrocytosis such as in the above instance is related simply to an increased percentage of reticulocytes, and that there might still exist an underlying spherocytosis to account for the moderately increased fragility. Dameshek and Schwartz<sup>30</sup> believe that an increased number of reticulocytes produce a "pseudomacrocytic" anemia, but that the various hemolytic anemias are generally related to the formation of spherocytes, probably as a response to the presence of isohemolysins. Although the writer's observations do not touch upon the latter question, they do reveal clearly that the mean erythrocyte diameter (M.C.D.) is not closely correlated with the reticulocyte percentage, in different instances of hemolytic anemia. This is illustrated by the following data:

	M.C.D.	M.C.V.	Retic. per cent	$H_1$
Case 1. Familial hemolytic jaundice.....	7.0 $\mu^*$	87.0	15.2	<0.7
Case 2. Familial hemolytic jaundice.....	6.9 $\mu^*$	104.0	27.6	<0.7
Case 3. Familial hemolytic jaundice.....	7.3 $\mu^*$	115.0	12.0	<0.7
Case 4. Familial hemolytic jaundice.....	6.9 $\mu^\dagger$			
	7.0 $\mu^*$	77.0	14.0	<0.7
Case 5. Reticuloendotheliosis; macrocytic hemolytic anemia.....	8.25*	111.0	4.6-7.0	0.54 (control 0.54)
Case 6. Splenic anemia; probable diffuse splenic fibrosis; macrocytic hemolytic anemia...	8.2	119.5	4.5	0.44 (control 0.48)
Case 7. Cirrhosis of the liver; mild macrocytic hemolytic anemia.....	8.4*	100.0	3.6	0.44 (control 0.48)
Case 8. Hemorrhagic ovarian cyst; severe macrocytic hemolytic anemia.....	8.8 $\dagger$	—	15.0	0.38 (control 0.38)
(Case described in foregoing)				

\* Bock erythrocytometer.

$\dagger$  Pijper halometer (C. Zeiss & Co.).

$H_1$  = concentration of salt solution in which hemolysis commenced in the fragility test.

The data given by Dameshek and Schwartz<sup>29</sup> for three cases of acute hemolytic anemia, also fail to reveal correlation between the M.C.D. and reticulocyte percentage. The values are as follows:

	M.C.V.	M.C.D.	Retic. per cent
Case 1		7.55	12.0
Case 2	125	7.44	20.8
Case 3	80	6.4	20.6

(The M.C.D. was determined in these instances by the Price-Jones curve.)

Thus it is clear that varying reticulocytosis does not explain the marked difference in M.C.D. noted between the cases of familial hemolytic anemia, and those that have been classified here as macrocytic hemolytic anemia. It is believed that there are many instances of the latter type, differing fundamentally from the familial or microcytic form, and that the term "pseudo-macrocytic" is not appropriate for these cases. Although reticulocytes are unquestionably larger than mature erythrocytes, the macrocytic tendency effected by them is not sufficiently great to interfere in the distinction of the two forms of hemolytic anemia, as described in the foregoing.

### RELATIONSHIP OF JAUNDICE AND ANEMIA

In considering the pathogenesis of jaundice and anemia, it is quite evident that three factors are of importance, at least insofar as the familial form of the disease is concerned. These are: (1) the more fragile erythrocytes, (2) hypersplenism, and (3) bilirubin excretory function of the liver. Of the three, it is clear that the second is of prime importance. Under normal conditions, certain animals have small erythrocytes which behave toward hypotonic saline in quite the same fashion as do the spherical microcytes of hemolytic jaundice patients. This is most marked in the goat,<sup>14a</sup> and yet the goat is not afflicted with jaundice, anemia, or splenic enlargement. Quite similarly, certain members of hemolytic jaundice families may go through life without developing any of these manifestations, although, as noted at the outset, they will often be found to have the characteristic spherocytes.

Although there can be no doubt that hypersplenism is responsible for excessive wastage of erythrocytes with resultant over-production of bilirubin, a comparison of the degree of jaundice and anemia in the present series of cases reveals clearly that these are not correlated phenomena and that the bilirubin excretory function of the liver must be regarded as the most important, probably the sole factor in determining the presence or absence of jaundice. Except during hemolytic "crises" jaundice and anemia are not proportional in degree; in fact, a distinct tendency toward an inverse relationship exists. In this regard it seems particularly noteworthy that the two extremes of jaundice or anemia in this series exhibited the most anemia and the least jaundice and vice versa. Thus, one case was that of a boy of 16 who came to the hospital because of profound anemia, but who was not, and never had been jaundiced. The icterus index was 8, the hemoglobin 20 per cent (17 gm. per 100 c.c. = 100 per cent); splenomegaly and spherical microcytes were found, and the feces contained 792.9 mg. of urobilinogen per day. Complete recovery from the anemia took place after splenectomy. In striking contrast to this case was a boy of 18

who presented himself because of jaundice without anemia and who was unwilling to consider splenectomy because he had never been sufficiently sick. The icterus index in this case varied between 45 and 92, while the hemoglobin ranged between 80 and 90 per cent. This patient, of course, typifies Chauffard's characterization,<sup>17</sup> "more jaundiced than sick." The contrast between these cases strongly suggests that relative liver dysfunction is somewhat of an asset in familial hemolytic icterus. Study of the urine urobilinogen in these patients offers further evidence of the more sluggish liver function in the cases whose jaundice is most marked. In general, much larger amounts of urobilinogen were found in the urine of patients with relatively little anemia, but much jaundice. On the contrary the amounts were normal or but slightly increased in those cases with much anemia and little or no jaundice. It may be emphasized that, contrary to common belief, urobilinogen is often not increased in the urine in patients showing even marked increase of blood destruction. The urobilinogen was not increased in the urine of the patient mentioned above, who suffered from severe (spherocytic) hemolytic anemia, without jaundice.

It should be pointed out that hemolytic "crises" usually constitute an exception to this tendency to an inverse relationship between jaundice and anemia. During these periods a parallel increase of jaundice and anemia is often seen. This is usually followed by some decline in the degree of jaundice together with a rapid increase in the hemoglobin and erythrocytes. For example, in one of the cases in the present series the hemoglobin fell from 54 to 45 per cent during three days of a mild hemolytic "crisis"; the icterus index rose from 20 to 32. In the next 13 days the hemoglobin rose spontaneously to 78 per cent, and the icterus index returned to 20.

#### AUTOHEMAGGLUTINATION

Widal and his associates<sup>18</sup> were the first to regard autohemagglutination as a distinguishing feature of acquired hemolytic jaundice. Although the experience in the present series appears to bear this out, inasmuch as it was observed twice in the acquired group and not at all in the familial cases, the phenomenon is, nevertheless, of doubtful reliability so far as this distinction is concerned. Thus, Masters and his associates<sup>19</sup> noted autohemagglutination in two cases of hemolytic jaundice in the same family. Both exhibited microcytes and increased fragility. Tileston<sup>20</sup> states that autoagglutination is rare except in hemolytic jaundice and that there may be a causal relationship, but a survey of the literature makes it clear that increased blood destruction and autoagglutination are by no means strictly correlated. In the above described case of acquired hemolytic jaundice in which increased hemolysis persisted for some time after splenectomy, the autohemagglutination was noted for an even longer period, in fact it was still present two months after the signs of increased blood destruction had disappeared. The phenomenon has been observed in a case of bronchopneumonia without anemia,<sup>21</sup> and in a pregnant woman with severe anemia



due to bleeding hemorrhoids.<sup>22</sup> The writer has recently noted its occurrence in a case of polycythemia vera. Here, however, it was not as marked as in the cases of hemolytic jaundice. In multiple myeloma, Reimann<sup>23</sup> was the first to observe autoagglutination. It appears to occur rather regularly in this disease and has been noted in each of the last five cases seen in the University of Minnesota Hospital. This form of autoagglutination, however, depends upon marked rouleau formation and differs further from that seen in hemolytic jaundice in that it is not affected by temperature; the agglutination of erythrocytes is not reversible at 37° C. Its occurrence in vivo is evidently prevented simply by virtue of the rate of blood flow; thus, in cases of multiple myeloma whose blood exhibited autoagglutination, Foord<sup>24</sup> was able to produce clumping of the erythrocytes in the retinal vessels simply by adequate pressure on the eyeball. As demonstrated first by Reimann,<sup>23</sup> the rouleau formation of multiple myeloma is on the basis of hyperglobulinemia, whereas the autohemagglutination due to "cold" agglutinins may occur to a marked extent when there is no abnormality in the plasma proteins. Thus, in the case of acquired hemolytic jaundice in this series, in which the autohemagglutination was the most marked, the plasma proteins were: Fibrinogen, 0.41 per cent, euglobulin 0.29 per cent, pseudoglobulin 1.55 per cent, albumin 3.92 per cent, total 6.17 per cent.

#### RELATIONSHIP OF THE SPLEEN TO THE NUMBER OF CIRCULATING ERYTHROCYTES

Barcroft's studies<sup>25</sup> revealed that the spleen in several species of animals serves as a reservoir for erythrocytes. To what extent his conclusions can be applied to the human spleen is not certain, but it is probable that temporary increases of erythrocytes produced by epinephrine are secondary to splenic contraction. It was possible recently to observe the effect of epinephrine on the spleen of a patient (not having hemolytic jaundice or anemia) who had previously been given thorotrast,\* and at the same time to note the variations in the number of circulating erythrocytes. By approximate estimation of the volume of the spleen, a definite reduction in size was estab-

Time in minutes after administration of 1 c.c. 1/1000 epinephrine subcutaneously	Erythrocytes in millions per cu. mm.	Estimated volume of spleen by X-ray. (100% = volume before administration of epinephrine)
0	3.57	100%
5		50%
10		50%
15	4.08	50%
20		70%
30	4.11	90%
40		100%
45	3.85	
60	3.64	

\* Unpublished study with Dr. Leo Rigler.

lished, and, as noted below, this was shortly followed by a temporary, significant increase in the number of circulating erythrocytes.

Doan and his associates<sup>5</sup> have called attention to the marked increase in hemoglobin and erythrocytes commonly observed within the first few hours after splenectomy. They ascribe this increase in part to the epinephrine administered preoperatively and in part to the elimination of inhibitory influences affecting the bone marrow. Data obtained in certain of the present series of cases of hemolytic anemia indicate that the preoperative effect of adrenalin is of itself quite adequate to explain this increase. The following observations were made as shown in table on page 1780.

In the above instance it was clear that epinephrine produced a rapid and considerable increase in hemoglobin and erythrocytes; after splenectomy this effect could not be reproduced.

In the following case, the data again suggest that excitement or emotional factors alone may suffice to bring about a significant elevation of hemoglobin and erythrocytes.

Date	Hemoglobin, per cent	Erythrocytes in mill. per cu. mm.
4-11 11:45 a.m.	51	2.30
1:15 p.m.	60	2.93
2:00-2:50 p.m.	Splenectomy accom- panied by blood transfusions.	{ Patient nervous and apprehensive before preoperative sedation.
3:00 p.m.	56	
5:00 p.m.	62	3.18
10:00 p.m.	61	3.13
4-12 9:00 a.m.	54	3.17
		2.77

The above observations indicate that the effect of epinephrine with consequent splenic contraction and liberation of erythrocytes to the circulation is quite adequate to account for the immediate postoperative increase in hemoglobin and erythrocytes.\* Although it is probable that some individual variation exists, the present observations indicate that, in carrying out splenectomy, epinephrine should be administered about one-half hour prior to clamping the splenic pedicle, if a maximum autotransfusion is to be obtained.

#### LIVER DISEASE AND HEMOLYTIC ANEMIA OR JAUNDICE

Increased blood destruction in association with liver disease has been referred to in some detail in a previous communication.<sup>30</sup> In the present series of cases, eight were included in whom this combination was observed. Seven of these were cases of cirrhosis of the liver, one was a patient with a severe, prolonged "catarrhal" jaundice. The latter was case 71 in the writer's previous report,<sup>30</sup> while six of the seven cases of cirrhosis were

\* Since this was written, similar studies of the effect of epinephrine have been carried out in four additional cases of familial hemolytic jaundice. In each instance the results were essentially the same as are given above.

	Date	Hemoglobin per cent	Erythrocytes in mill. per cu. mm.	
(Case 1)	6-13	56	2.0	Patient angry and disturbed because she was told that splenectomy had been postponed.
	6-15	72	3.5	
	6-16 8:30 a.m.	64	2.7	
	8:35 a.m.	0.5 c.c. 1/1000 epinephrine		
	6-16 9:30 a.m.	73	3.5	
(Case 2)	8-6	62	3.3	
	8-7	63	3.3	
	8-8	60	3.0	
	8-9 10:00 a.m.	67	3.5	
	10:30 a.m.	67	3.49	
	11:00 a.m.	65	3.23	
	11:05 a.m.	0.5 c.c. 1/1000 epinephrine		
	11:35 a.m.	81	4.18	
	12:05 p.m.	75	3.88	
	12:35 p.m.	71	3.6	
	1:35 p.m.	60	2.96	
	2:35 p.m.	66	3.52	
	5:35 p.m.	65	3.32	
	8-10	66	3.37	
	8-11	Splenectomy—uneventful recovery (epinephrine given just prior to operation)		
	8-23 9:00 a.m.	75	4.8	
	9:30 a.m.	74	5.2	
	10:00 a.m.	74	5.3	
	10:10 a.m.	0.5 c.c. 1/1000 epinephrine		
	10:40 a.m.	75	5.28	
	11:10 a.m.	74	4.32	
	11:40 a.m.	70	5.08	
	12:40 a.m.	70	4.2	
	1:40 p.m.	70	4.08	
	4:40 p.m.	71	4.8	
(Case 3)	2-25 10:00 a.m.	47	2.51	
	10:00 a.m.	0.5 c.c. 1/1000 epinephrine		
	10:15 a.m.	53	3.26	
	10:30 a.m.	57	3.71	
	10:45 a.m.		3.70	
	11:30 a.m.	59	3.60	
	2-28 10:00 a.m.	50	3.30	
	10:00 a.m.	0.5 c.c. 1/1000 epinephrine		
	10:15 a.m.	63	3.35	
	10:30 a.m.	63	3.55	
	10:45 a.m.	62	4.35	
	11:00 a.m.	59	3.28	
	11:30 a.m.	52	3.00	
	3-8	Splenectomy—uneventful recovery (epinephrine given just prior to operation)		
	3-16 10:00 a.m.	84	6.34	
	10:00 a.m.	0.5 c.c. epinephrine		
	10:15 a.m.	86	6.22	
	10:30 a.m.	86	6.46	
	10:45 a.m.	88	6.75	
	11:00 a.m.	84	6.42	
	11:30 a.m.	84	6.22	

numbers 70, 72, 73, 74, 75, and 76. The seventh has been observed subsequently; in this case there was a slight increase in the rate of blood destruction with mild jaundice, but without anemia. The patient, a male 68 years

of age, was found to have ascites, enlarged spleen and liver. The icterus index ranged from 13 to 16. The hemoglobin was 91 per cent (100 per cent = 17 gm. per 100 c.c.) The feces urobilinogen was 274 mg. per day, the amount in the urine ranging from 19 to 45 mg. daily (normal 0-4), so that the total urobilinogen excretion was definitely in excess of the upper limit of normal, which was found to be 280 mg. per day.<sup>3b</sup> In the earlier study, data were given for each of the cases of the above numbers, so that it is unnecessary to repeat this at present. Case 74 in the previous series has been studied on two subsequent occasions, and the later findings\* require further mention. This patient had the most severe anemia of any in the group of eight. In 1933 a prolonged "hemolytic crisis" occurred from which the patient eventually recovered and following which she remained fairly well until 1937. A moderate amount of ascites was noted in 1934. About this time the patient left the vicinity and was not seen again until the spring of 1937. She was now 71 years of age. Mild icterus and anemia had recurred; the hemoglobin was 60 per cent, and the icterus index 18. Splenectomy was recommended but refused. The patient left the hospital and was not seen again until August 13, 1937. At this time the anemia had markedly increased; the hemoglobin was 35 per cent, icterus index 43, feces urobilinogen 1660 mg. per day, urine urobilinogen 9.3 mg. per day. From 8-13 to 8-22 the patient was observed in the hospital and received occasional blood transfusions without appreciable benefit. The hemoglobin level gradually declined to 25 per cent. Splenectomy was decided upon, and accordingly, 3000 c.c. of citrated blood were given by drip transfusion during a 48 hour period. Just prior to operation the hemoglobin was 53 per cent, and the patient's condition appeared distinctly improved. Splenectomy was carried out by Dr. W. T. Peyton. The spleen weighed 880 gm. The liver was enlarged and quite cirrhotic. The peritoneal cavity contained at least a liter of clear, yellow fluid. For the first two post-operative days the patient's condition was good. On the third day, however, she became rapidly dyspneic and irrational, and evidence suggestive of atelectasis, pneumonia, or a combination was noted in the left lower lobe. Death occurred on the fourth day after operation. At necropsy† the entire left lower lobe was atelectatic, and there were areas of atelectasis in the left upper and right lower lobes. No pneumonia was observed either grossly or microscopically. The liver weighed 1835 gm. It was firm, yellowish brown and diffusely cirrhotic. The bone marrow in the shaft of the femur was red. Microscopic examination of the liver revealed a moderate degree of portal cirrhosis with marked periportal lymphocytic infiltration. The liver was quite fatty. The bone marrow exhibited normoblastic hyperplasia. Sections of the spleen revealed a remarkable prominence of the sinuses, quite similar to the "sinus hyperplasia" which was emphasized by Dürr<sup>26</sup> as a frequent finding in primary splenic fibrosis. Dürr regarded this as a fea-

\* These were referred to in part on page 1787.

† The writer is indebted to Dr. Ambrose Herzog of the Department of Pathology, University of Minnesota, for a report of the necropsy findings.

ture serving to separate Banti's disease from splenic enlargement secondary to cirrhosis of the liver. This could not be corroborated by the writer.<sup>27</sup> In the present instance it was impossible to decide whether the changes had been primary in the liver or spleen.

The eight cases mentioned above, in which evidence of blood destruction accompanied liver disease, were encountered in a group of 59 patients; 38 of these were believed to have cirrhosis of the liver, whereas 21 were classified as cases of "catarrhal" jaundice. Superficially, this suggests that the occurrence of increased blood destruction with liver disease is relatively rare. A considerable number of the patients, however, had marked "regurgitation" jaundice, with direct Van den Bergh reaction and bilirubinuria. In this group, of course, urobilinogen excretion in the feces is no longer of value in measuring the rate of blood destruction, except where the values are distinctly elevated in spite of a diminution in the outflow of bile.

The cases of Hodgkin's disease and leukemia associated with hemolytic anemia have been referred to elsewhere,<sup>30, 28</sup> so that this subject need not be considered further at this time.

#### SUMMARY AND CONCLUSIONS

1. Observations made in a series of 35 cases of hemolytic jaundice or anemia are discussed. Twenty of these cases were of microcytic type, 15 were macrocytic. Two of the latter group exhibited persistence of hemolytic anemia in spite of removal of associated pathologic conditions which might have been considered causal; in one of these cases splenectomy later resulted in cure.

2. Of most significance in distinguishing the familial or congenital from the secondary or acquired type is the predominance of microcytes in the former, and of macrocytes in the latter. This distinction should depend upon measurement of the average diameter of the erythrocytes, not upon simple inspection of the blood smears. Increased fragility was uniformly encountered in the congenital cases but was also observed in two of the patients with liver disease who had macrocytosis and increased blood destruction. Autohemagglutination was observed in two cases of macrocytic hemolytic anemia but in none of the cases of the familial variety.

3. In this series, jaundice and anemia were not found to increase in parallel fashion. Except for periods of hemolytic "crises" the opposite tendency was observed. In general it was true that the more jaundiced patients were the least anemic; in fact, the most jaundiced patient in the series was the least anemic, whereas the most anemic individual was not jaundiced. This suggests that a sluggish bilirubin excretory function of the liver, instead of being detrimental, may actually be of benefit in tending to prevent anemia.

4. The marked increase in circulating erythrocytes which is often observed immediately after splenectomy, is adequately explained by the pre-

operative effect of epinephrine on the spleen. Increases of the same magnitude may be produced with epinephrine in hemolytic jaundice before splenectomy. After operation the effect was not obtained.

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# CLINICAL STUDY OF THE ETIOLOGY OF OBESITY \*

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OBESITY is attributed to exogenous factors in most instances, but a few cases are thought to be of endogenous origin. Such appears to be the prevailing concept of the etiology of the malady. Newburgh,<sup>1</sup> on the other hand, contends that all cases of adiposity are caused by an energy intake which exceeds that of the body requirements. Factors favoring an excessive food intake have been studied by Harrington,<sup>2</sup> and Newburgh. They have noted the frequency of bad food habits and of desire for concentrated foods in obese patients. The activity of the patients during the gain in body weight, however, has been more or less neglected.

Endogenous adiposity has been attributed in most cases to alteration of the thyroid, pituitary or ovarian secretions, or to lesions in the hypothalamus.

The present study is concerned with, first, alterations in caloric intake or caloric requirement during the gain in body weight in obese patients; second, the incidence of evidence of ovarian dysfunction; third, the relationship of change in body weight to the onset of certain diseases of the hypothalamus and thyroid and pituitary glands; and fourth, the ability of obese patients to lose body weight when low caloric diets are followed. Cases of myxedema, pituitary tumor and chronic encephalitis were selected because corpulence in these diseases is usually cited to support the contention that alteration of the secretions of the thyroid and the pituitary glands or lesions in the hypothalamus are etiologic factors in obesity. Cases of two other diseases in which lesions of the hypothalamus may occur (suprasellar tumors and diabetes insipidus) were included.

## METHOD OF STUDY

The records of 350 cases of obesity, of which about one-third were personally observed, were studied for evidence of an increase of food intake or a decrease of activity during the time of gain in body weight. It is appreciated that histories of food intake are notoriously unreliable, but in a few instances the circumstances described by the patient justify the conclusion that there was an increase of food intake. A history of diminished activity is usually definite, particularly if it is caused by a long illness or convalescence. Ovarian dysfunction was considered to be present only if there was a history of abnormal menstruation.

The records of 100 cases of chronic encephalitis, 24 cases of myxedema, 22 cases of pituitary tumor, five cases of suprasellar tumor and seven cases

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of diabetes insipidus were analyzed for the incidence of obesity and for changes in body weight following the onset of the malady. Encephalitis had been present for at least one year in all instances, and the other diseases had existed for four months or longer.

The number of those obese patients who were known to have followed low caloric diets for a sufficient time and the percentage of those who lost weight satisfactorily were ascertained. The daily caloric value of the prescribed diets varied from 800 to 1500, but in all instances it was at least 1000 calories less than the patient's estimated 24 hour requirements. Such diets were followed for periods varying from one month to two years.

## RESULTS

Sufficient data were available regarding the food intake and activity during the gain in body weight in 154 cases. Gain in weight was associated with pregnancy or pregnancies without a history of increase in food intake or diminished activity in 32 instances. Most of these patients gained 15 to 25 pounds with each pregnancy, maintained the added weight, and thus became obese after three to six pregnancies. There were 13 patients who were either always obese or became obese without a history of change in activity or food intake. The gain in body weight which occurred simultaneously with diminished activity in 104 instances was accounted for in five cases by change in occupation, and in 99 others by a long illness, disability or convalescence. Accidents produced disability lasting from several months to two years in seven patients, a history of a long illness or convalescence following an operation was obtained in 17, a history of a long illness following pregnancy was present in 20, and 54 were ill or disabled for periods varying from months to years with psychoneurosis, heart disease, varicose veins, arthritis, hypertension, painful feet, diseases of the eyes which interfered with vision, residual paralysis after anterior poliomyelitis, etc.

Of 300 women, sufficient data regarding menstruation were available in 289. The menses were normal in 143 cases. Forty-eight had passed the menopause, but the obesity began several years prior to the change of life, and the menses had been normal during that time. In 191 cases ovarian dysfunction could apparently be excluded as an etiologic factor in the adiposity. Obesity began before puberty in five cases, but menstruation was normal. Adiposity began after the menopause in 15 instances, and antedated it in two. In these cases, however, the menses had been irregular for years. Menstruation was irregular in 34 patients and in four of these became irregular between the ages of 45 and 48 years after long standing adiposity. The menses were absent in 13, scanty in five, painful in seven and excessive in seven. The data are shown in table 1.

The incidence of obesity in myxedema, pituitary tumor, chronic encephalitis, suprasellar tumor and diabetes insipidus, and the relationship of

TABLE I

The incidence of, and types of, menstrual disorders, and the relation of onset of obesity to menopause and puberty are shown in the table. The number of these patients with various menstrual disorders who lost body weight when low caloric diets were followed is also shown.

Menstrual History and Relation of Menopause and Puberty to Onset of Obesity	Number	Number of Patients Who Lost Weight on Low Caloric Diets
Normal.....	126	60
Irregular.....	34	20
Nearing menopause.....	4	2
Dysmenorrhea.....	7	2
Menorrhagia.....	7	4
Scanty.....	5	4
Amenorrhea.....	13	6
Menopause.....	74	10
Obesity began after.....	15	6
Obesity began before.....	50	3
Menses were normal.....	48	3
Menses were abnormal.....	2	—
Artificial because of fibroids.....	4	1
Puberty.....		
Obesity began before.....	22	16
Menses normal.....	17	12
Menses abnormal.....	5	4
Obesity began with.....	1	1
Menses irregular.....	1	1

changes in body weight to the onset of these maladies are shown in table 2. It is to be noted that although the incidence of corpulence is high in these diseases, it was present in most cases before the onset of the other malady. It is also to be noted that patients with myxedema, pituitary tumor or chronic encephalitis became either more, or less, obese. Approximately as many patients lost weight as gained weight after the onset of myxedema and pi-

TABLE II

Shows the nutritional status of the patients at the time of examination, the relation of the obesity and the changes of body weight to the onset of the other maladies.

	Myxedema	Pituitary Tumor	Chronic Encephalitis	Suprasellar Tumor	Diabetes Insipidus
Nutritional status					
Obese.....	6	7	16	1	1
Thin.....	1	4	19	2	1
Normal.....	11	7	52	2	5
Relation of obesity to the onset of					
Antedated.....	4	5	16	1	1
Postdated.....	3	3	5	0	0
Disappeared with.....	1	1	5	0	0
Changes in weight after onset of					
Gained.....	6	5	6	1	0
Lost.....	5	7	33	2	1
No change.....	8	6	16	2	6

pituitary tumor, and loss of weight was five times more prevalent than gain in weight after the onset of chronic encephalitis. The patient with obesity and suprasellar tumor was obese for years before the cranial lesion produced any symptoms and continued to gain weight afterwards, whereas the patient who was obese prior to the onset of diabetes insipidus did not continue to gain weight.

Low caloric diets were known to have been followed for an adequate time by 146 patients, and all of them lost body weight satisfactorily. Several patients did not lose weight on low caloric diets at home, but in all instances they lost weight during and after hospitalization on the same diet. It is to be noted from tables 1 and 3 that the patients who lost weight on low caloric diets included those who had various menstrual disturbances, those who became obese from unknown causes and those who became corpulent with pregnancy, illness, operation, myxedema, pituitary tumor, chronic encephalitis and increased food intake. Adiposity developed in association with 36 different diseases or disabilities in the patients known to have lost weight satisfactorily. The patients listed under illness, table 3, became

TABLE III

Shows that obese patients who will follow low caloric diets for an adequate time will lose body weight regardless of the coexisting disease or the circumstances associated with the onset of the obesity.

Obesity Began in Association with	Number Who Lost Weight on Low Caloric Diets
Pregnancies . . . . .	22
Illness . . . . .	23
Impaired locomotion . . . . .	15
Operations . . . . .	10
Increase of food intake . . . . .	2
Chronic encephalitis . . . . .	3
Myxedema . . . . .	1
Hypophyseal tumor . . . . .	1
Insufficient data or negative history . . . . .	69

obese with heart disease, psychoneurosis, depressive psychosis and after long convalescences following pneumonia and typhoid fever. Those listed under impaired locomotion became obese in association with ununited fractures of legs, paralysis of legs following anterior poliomyelitis, painful feet, varicose veins, arthritis and impaired vision. The operations associated with gain in weight in these patients were cholecystectomy, appendectomy, thyroidectomy, removal of ovaries or ovarian cysts, hysterectomy and abdominal operations undertaken for reasons unknown. The patient with myxedema became obese after the onset of hypothyroidism. She remained in the hospital for one month on a low caloric diet without thyroid medication and lost 10 pounds in body weight. The patient with pituitary tumor and the two patients with chronic encephalitis also developed their obesity after the onset of these diseases, and all three lost weight satisfactorily.

## DISCUSSION

The high percentage of patients who gave a history of diminished activity while they were gaining weight indicates that many cases of "endogenous" obesity would be eliminated by a more detailed history. Illness or convalescence diminished the activity in most instances and corpulence very likely could have been prevented in these cases. It is just as important to prevent obesity as it is to relieve it, yet this phase of the subject has been emphasized comparatively little. The development of obesity with pregnancies in 20 per cent of these cases demonstrates the value of the practice of prevention of excess gain in body weight with pregnancy which has long been stressed. Corpulence could have been prevented in many of the 131 patients who became obese with pregnancies or with illness and convalescence. Adequate nutrition during a long illness or convalescence does not signify that the patient must become obese.

The theory that hypothyroidism is of etiologic importance in obesity has been discarded generally, but when adiposity develops in myxedema the lowered metabolism is usually considered to be an etiologic factor. The findings of this study indicate that the diminished metabolism is of little consequence in the etiology of the obesity. Patients with myxedema may gain or lose weight. A history of diminished activity with little or no impairment of appetite was obtained from two of the three patients who became obese after the onset of myxedema. Patients with coexisting myxedema and obesity will lose body weight satisfactorily when low caloric diets are followed for an adequate time.

The classic description of adiposity associated with hypophyseal tumor by Froelich<sup>3</sup> directed attention to the pituitary gland in certain cases of obesity. Many such cases have appeared since in the literature. The fact that as many of these patients lost as gained weight might be accounted for by a difference of pituitary secretions in hypophyseal tumors. The hormone liberated by the pituitary may be increased, normal or diminished in these cases. A history of diminished activity with a good appetite was obtained, on the other hand, from all those patients who became obese after development of hypophyseal tumor. One of these was known to have followed a low caloric diet and lost body weight. Such observations cast some doubt upon the etiologic importance of alteration of the pituitary secretions in the obesity of these patients.

The hypothalamus was incriminated in certain cases of adiposity when Smith<sup>4</sup> found that removal of the hypophysis in rats did not produce obesity unless the tuberal region was injured. Many case reports of obesity associated with chronic encephalitis have appeared in support of this contention. The development of obesity in five cases and its disappearance in five other patients after the onset of chronic encephalitis might be attributed to a different distribution and intensity of the brain lesions. A history of diminished activity with a good appetite was obtained, however, from three of

the patients who became obese after the encephalitis developed, and two cases in which encephalitis antedated the obesity were known to have followed low caloric diets and lost weight satisfactorily. Such findings indicate that encephalitic lesions of the hypothalamus played a minor rôle, if any, in the production of obesity in these cases. In addition, lesions of the hypothalamus apparently were not important factors in the production of adiposity in our cases of coexisting obesity and diabetes insipidus or suprasellar tumor. It is difficult to detect any difference between the obesity which develops in association with long inactivity due to a fractured leg and that which develops with a long illness due to pituitary tumor, suprasellar tumor, chronic encephalitis or myxedema. One has to admit, however, that not all patients with fractured leg, etc., become obese, but neither do all cases of myxedema, pituitary tumor and chronic encephalitis.

It is difficult to ascertain from the data available whether or not ovarian dysfunction was present in the patients with abnormal menses. The relationship of menstrual disturbances to obesity is also difficult to evaluate. Data are not available regarding the percentage of patients with menstrual disorders who become obese. Large numbers of these patients never gain excessive body weight. Amenorrhea, on the other hand, is not a common symptom and has been regarded as evidence of ovarian dysfunction. This symptom existed in six patients personally observed, and in all instances the menses returned after the loss of 10 to 100 pounds in body weight. The weight loss was accomplished by following low caloric diets without endocrine medications. Ovulation undoubtedly occurs in some of these cases of adiposity and amenorrhea. One such patient had not menstruated for seven years, yet she had three normal pregnancies at 1½ and two year intervals during that time. Another had amenorrhea for 2½ years prior to her last pregnancy. Ovarian dysfunction as an etiologic factor in the obesity of these cases is doubtful in view of the fact that patients with the different menstrual disorders lost body weight when low caloric diets were followed.

#### SUMMARY

The records of 350 cases of obesity have been analyzed for a history of increase of food intake or diminished activity during the time of gain in body weight, for evidence of ovarian dysfunction and for the ability of these patients to lose body weight on low caloric diets. In addition, the records of 100 cases of chronic encephalitis, 24 cases of myxedema, 22 cases of pituitary tumor, five cases of suprasellar tumor and seven cases of diabetes insipidus were analyzed for the incidence of obesity and for the changes in body weight following the onset of the malady.

Inactivity occurred simultaneously with gain in body weight in 67.5 per cent. A history of an increase in food intake, on the other hand, was obtained in only 3.2 per cent. A long illness or convalescence produced the

inactivity in 64.3 per cent. Ovarian dysfunction as evidenced by abnormal menses or menopause was present in 50.6 per cent.

The incidence of obesity in myxedema, pituitary tumor and chronic encephalitis was high, but adiposity antedated the other malady in most instances. The number of patients who lost body weight equaled approximately those who gained weight after the onset of myxedema and pituitary tumor. After chronic encephalitis developed, on the other hand, loss of weight occurred approximately five times as frequently as did gain in body weight. The etiologic rôle of alteration of the thyroid, pituitary and ovarian secretions, and of lesions in the hypothalamus is discussed.

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# MEDICO-LEGAL PROBLEMS OF HYPOGLYCEMIC REACTIONS IN DIABETES \*

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## INTRODUCTION

THE medico-legal aspects of insulin reactions in diabetics have not aroused the deserved interest in the medical world. Only two reports<sup>1, 2</sup> on this subject could be found in the literature. Despite the experience of physicians with the bizarre psychotic manifestations of hypoglycemia in their diabetic patients and the legal conflicts arising therefrom, it is surprising that the medical profession has neglected reporting such cases. Thus it is that 15 years after the introduction of insulin therapy there is still no standard legal precedent or procedure to handle such incidents.

There is, also, a profound sociological problem involved in each individual susceptible to hypoglycemic mental changes. His relation to the family, occupational group and society in general may have to be altered and adjusted adequately. His economic and social status may be disrupted by necessary restriction of his occupational activities to a limited field.

The increasing importance of this problem is apparent in the light of the continuously mounting incidence of diabetes and the increasing use of insulin among diabetic patients. This has been due to the wider acceptance of insulin therapy by patients and physicians and, in addition, to the advent of protamine insulin which has added many thousands to the ranks of those using insulin.

## OCCURRENCE OF HYPOGLYCEMIC REACTIONS

Every diabetic patient taking insulin, even though well controlled, may be subject to hypoglycemic reactions because of general intrinsic changes in tolerance as well as extrinsic, though transitory, factors such as sudden emotional expression, increased exercise, omission of meals, etc. Naturally, the poorly controlled diabetic with marked irregularity of the blood sugar level is more subject to reactions. It is obvious that the uncoöperative, "wild" diabetics, who exceed their dietary limitations or fail to adjust their insulin supply to the diet, will always present difficulties in management. In this group of poorly controlled patients, there must be included the "resistant" diabetic in whom the margin of safety between control and insulin overdosage is so narrow that hypoglycemic reactions are always imminent.

On the whole, the introduction of protamine insulin has reduced the incidence of hypoglycemic reactions. One is struck, at times, by the severity of the reaction with protamine insulin, apparently due to the prolonged release of insulin from the injection site. In addition, reactions with prota-

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mine insulin often lack those familiar premonitory symptoms such as palpitation, sweating, asthenia, etc., which warn of and prepare the patient for an impending shock. Further, the pressure of daily life with the possibility of disruption of the meal schedule may make the use of protamine insulin more hazardous in susceptible and very active patients because of its continuous action.

### NEUROLOGICAL SYNDROME OF HYPOGLYCEMIA

The somatic symptoms of hypoglycemia, though important in precipitating legal complications, are overshadowed by the nervous and mental changes which contribute most to our topic. Interestingly enough, the somatic and central nervous system manifestations of hypoglycemia resemble strikingly the symptoms seen in high altitudes in mountain climbers, aviators, etc., where diminished atmospheric oxygen tension with resultant anoxemia is the acknowledged etiological factor. The analogy is now understood in the light of investigations<sup>3</sup> which have demonstrated a distinct decrease in oxygen utilization by the brain tissue during hypoglycemia. The neurological phenomena of hypoglycemia begin with vertigo, diplopia, tremor, and ataxia. Then follow paresthesias and hypalgesias, aphasia, twitchings, and rigor. Weakness or paralysis of any muscle group in one or more limbs, convulsions, epileptiform seizures, complete unconsciousness and deep coma are the final manifestations. One group, the "monosymptomatic," manifests the hypoglycemic reaction predominantly by one symptom, such as a tic, or diplopia, etc., whereas a variety or range of symptoms may be found in the "polysymptomatic." Furthermore, there are some who present a stereotyped repetition of symptoms with each episode, while others may display utterly different manifestations with each reaction.

### MENTAL CHANGES

1. *Mild Cases.* There is a wide variety of mental changes displayed during hypoglycemia, from mild anxiety or exhilaration to severe psychotic states. The mild group of symptoms is initiated by irritability, anxiety, depression, exhilaration, or excitability. *Witzelsucht* and garrulity are rather infrequent. Partial disorientation and confusion, tendency to dawdle or loiter, and slowness of thought and action are commonly observed. Lack of will power and inability to make simple decisions may lead to typical *folie de doute* or *Entschlusslosigkeit*.

Any observer of diabetic patients could report countless examples of such mild mental manifestations. Therefore, only a few characteristic types will be cited for illustration. Relatives of some younger diabetics recognize the appearance of irritability, excitability, or hilarity as indicative of impending shock, and hence are experienced in taking prompt measures to abolish the reaction. Some diabetics appear morose, sullen and embittered, even asocial and misanthropic at the beginning of a hypoglycemic reaction. They



may refuse to sit with their families at the table or to engage in conversation and may even leave their company for the isolation of the bedroom. Here should be mentioned those children whose conduct may vary in the morning and afternoon classes in such a way, that ordinarily excellent and attentive pupils may exhibit inattention and misconduct during mild hypoglycemia. Exceedingly polite and considerate patients may display very rude and boorish behavior for short periods of time when hypoglycemic, and thus may jostle and push aside people on the street, without any evident reason, and in contrast to their normal demeanor, without even apologizing.

Some patients may have difficulties because of the slowness of thought and action accompanying hypoglycemia, and thus may arouse criticism from their foreman or employer. This is more significant in those patients whose work requires particular skill, such as weavers, seamstresses, typists, stenographers, etc.

The lack of will power and inability to make even the simplest decision is exemplified in those cases that, finding themselves on the threshold of hypoglycemia, are unable to take the food or sugar usually carried for such emergencies, even though this be in the pocket or in the hand. Many confusional and aphasic syndromes are reported by patients and their families, as typified by an incident wherein a boy misnamed the dishes at the dinner table, asking for ice-cream while indicating the butter, etc. Since this had happened before, the family recognized the cause and was able to abolish the reaction by feeding him sugar. Some children may use abusive language, or scold and berate their teachers, parents, or friends, such action presenting a transition to the more severe forms of hypoglycemic reaction.

Such mental changes may bewilder acquaintances and relatives who, familiar with the normal personality of the patient, are alienated by such strange and unusual actions. This abnormal behavior may give rise to serious social complications. The patient may be excluded from his circle of friends, business groups, or societies. The reaction may lead to very serious estrangements in the family with legal consequences. In one of our patients such bizarre behavior constituted sufficient grounds for a divorce action. Tillgren<sup>4</sup> reports a similar case in which hypoglycemic reactions caused the wife to ask for a divorce from her diabetic husband.

*2. Moderately Severe Cases.* The intermediate group of hypoglycemic mental changes presents exaggeration of the symptoms observed in the milder cases. Here are seen increasing difficulties of speech, thought, and action. Perseveration, confabulation, negativism, psychomotor hyperactivity, and pseudo-hysterical pictures up to hysterical opisthotonus are further manifestations. Maniacal behavior, acts of violence, exhibitionism, sexual perversity, compulsive laughter and crying, and impulsive actions follow increasing disorientation and confusion. Wanderings, delusions, hallucinations, melancholia, and paranoia, etc. are transitions to the severe group. As was pointed out in the neurological manifestations, here too, some patients may present one or two psychic pictures, and others a kaleidoscopic combina-

tion and variety of many of the above mentioned symptoms. This group is frequently characterized by partial or complete amnesia for actions committed during hypoglycemia.

In view of the limitation of space, only a few striking illustrations of this group will be presented. Many physicians have experienced difficulties in treating hypoglycemic reactions because of the negativism so common to this group. Not only may a patient refuse to take food himself, but he may even resist efforts by the physician, nurse or family to force food into him (R. M. Wilder<sup>13</sup>). It is not unusual for otherwise friendly and coöperative patients to strike physicians and nurses, when the latter attempt to administer treatment for the hypoglycemic reaction, and at times despite assistance, physicians have even been unable to administer glucose intravenously to such patients when violent agitation and partial confusion were manifest. In these cases it has been necessary to overpower the patients in order to permit the administration of glucose by the intravenous or oral route (stomach tube). A bizarre instance of negativism has been reported by Wauchope<sup>5</sup> in a man who insisted on driving his car home, with one eye shut (to obviate the diplopia), rather than eat the chocolate he carried with him.

Even more striking acts of violence and aggressiveness are common during hypoglycemia and may give rise to misdemeanor and assault. Thus, one of our patients, a very devoted mother, during hypoglycemia stuck a pin into her infant son's eye several times, mishandled and strangled him; only the intervention of her family prevented more serious injuries to the child. Kepler and Moersch<sup>14</sup> report the case of a severe diabetic who, while hypoglycemic, proceeded to shoot at his brother until he had emptied all the chambers of his gun. Fortunately he failed to inflict any injury. Another patient, an intelligent, well-mannered woman, has often been considered intoxicated when hypoglycemic in public because of her ataxia, confusion, abusive language, and belligerence.

Some patients, in a fury of devastation, break and shatter dishes, furniture, and household objects within their reach. One mother tearfully recounts the story of her diabetic son who in hypoglycemic frenzy smashes only expensive and prized possessions, such as a cherished vase or a valuable mirror. These cases reveal a certain amount of deliberateness or perhaps a kind of "pathologic logic" which directs the unconscious impulsive actions.

The release from inhibitions of moral, religious, or educational nature may allow full expression of repressed desires and pathological "drives." Exhibitionism during hypoglycemia is not uncommon. One of our younger diabetics undressed in public to the astonishment of bystanders. The earliest reports of insulin reactions by Oppenheimer,<sup>6</sup> Elias and Goldstein<sup>7</sup> related similar exhibitionistic tendencies. Other sexual aberrations have been observed. One severe diabetic, a young adult male, is greatly distressed by the hypoglycemic episodes which occur during or after coitus. Frequently the sexual act culminates with the patient in profound hypoglycemic shock, necessitating the immediate administration of sugar. More disturbing to

the patient and his wife, however, are the bizarre, sadistic, sexual perversions to which he is sometimes subject when hypoglycemia develops during intercourse. On recovery he is overcome with deep shame and embarrassment, inasmuch as his sexual habits are ordinarily normal. At times, because of partial or even complete amnesia, only the attitude and reaction of his wife, and the presence of bruises and scratch marks on her body, indicate to him that his behavior has been abnormal.

One of our patients, a 25 year old female, displays a variety of symptoms when hypoglycemic, acting as if intoxicated, becoming abusive and violent and on several occasions has outraged her family by defecating on the living room floor. Sexual abnormalities due to hypoglycemia have been reported here somewhat more fully in view of their obvious forensic importance. Except for exhibitionism, no attention has been paid to their significance heretofore.

The release from inhibitions during hypoglycemia may result in various actions foreign to the normal personality of the patient and may also be the basis of impulsive actions. An ordinarily moral and fanatically religious man has been known to blaspheme and abuse the church and God, astounding members of his congregation who could not understand the sudden change in his faith. A striking example of a compulsion during hypoglycemia was observed in one of our patients who was seized by an uncontrollable and irresistible urge to run through fast moving automobile traffic. With tremendous muscular effort he managed to cling to a lamppost, thus averting a serious accident. Such action might have accounted for the case of hypoglycemia reported by Sonne,<sup>8</sup> a diabetic who was struck by a trolley.

With further confusion and disorientation, the hypoglycemic patient may develop a *fugue* or "wandering state" which may last for a few hours. Even a keenly alert patient may not recognize the relationship of such mental clouding to the use of insulin, and may be ashamed to confess such an experience. One patient seized by a reaction while on his way to school wandered back home entirely disoriented, believing himself to be on the way to school all the time. Another case, while walking with his wife, apologized, left her abruptly and wandered about aimlessly for several hours, finally regaining mental clarity. On returning home he showed a complete amnesia for the events of the preceding hours.

It is evident that all these cases could have become involved in legal difficulties, were not their families or friends nearby to explain their actions on the basis of hypoglycemia. Such acts as destruction of property, assault, and sexual perversion are ordinarily subject to criminal law, and it is only because of the fact that patients commit them at home or among friends that they escape arrest. One of our patients, aware of the development of hypoglycemia, went to a candy store. There her violent agitation and loud demands for candy aroused the proprietor's suspicions that she was drunk. His refusal to sell her any candy made her so rabidly violent and abusive that her arrest was considered by the summoned policeman. Fortunately

her muscular activity resulted in an amelioration of the reaction, with restoration of her normal conduct, and with profuse apologies she was able to explain the hypoglycemic basis of her actions and avoided arrest.

3. *Severe Cases.* In this group of reactions we find intensification of the symptoms mentioned heretofore, up to completely psychotic states. Here, the complete disorientation and confusion, and the almost consistently complete amnesia, are characteristic features. The picture may resemble paranoia,<sup>9</sup> mania,<sup>6, 8, 9, 10</sup> catatonia, acute alcoholic delirium, Korsakoff's psychosis,<sup>11</sup> melancholia, etc. Naturally, the appearance of such severe syndromes is met with less often today because of the adequate training of the patients and their families, so that the usual therapeutic measures are taken before this stage is reached. These cases are so obvious that description is unnecessary. Some may be admitted to psychiatric institutions; one patient, a known diabetic with recurrent nocturnal maniacal episodes, so alarmed his family that in ignorance of the underlying hypoglycemia they called the police and had him transferred to a psychiatric hospital. Fortunately the transitory nature of such episodes precludes misinterpretation as to their etiology for more than a few hours, and the short course usually prevents very serious complications; nevertheless, during such episodes, even more than in milder confusion stages, actions may be committed which bring the diabetic face to face with the law.

#### FORENSIC SIGNIFICANCE

We have already referred to examples of hypoglycemic episodes in which legal complications arose. The first medico-legal case was reported by Fog and Schmidt<sup>1</sup> in 1931, nine years after the adoption of insulin therapy. Their patient, a truck driver, developed hypoglycemia while driving, and a serious accident occurred. By court order his driver's license was revoked because, in the opinion of the court, he did not possess the requirements of the Danish traffic law "as far as the mental abilities of an automobile driver are concerned." The next year, 1932, two cases were reported by Adlersberg.<sup>2</sup>

*Case 1.* K., 51 years of age, a very sedate business man, had been taking insulin for six years. After the usual injection of 30 units at 7:30 a.m. and breakfast, he went to his office one day and performed routine work. About 10 a.m. he took some fruit, and then made a few calls. At noon he went home for lunch by trolley. He had already had a "light dizzy feeling," and his companion told him the next day that he was amazed at the silliness and incoordinated movements of the patient at that time. The patient felt the need for sugar which, incidentally, he always carried with him but he lacked the "power and will" to take it. What happened thereafter he could not recall. The conductor and the police officer agreed as to the following: K. entered the trolley behaving like a drunkard, opened his vest, set his hat on the side of his head, yelled and laughed. The perplexed conductor called the police officer who ordered K. to leave the trolley with him. K. was obviously confused, resisted stubbornly, and had to be overpowered by the policeman who dragged him by force to the police station, followed by a curious crowd. He was rabidly violent.

Some time later, with decreasing disorientation and confusion, he begged the police to obtain some bread for him. This done, he was soon in complete possession of his senses, greatly surprised at his arrest and his preceding actions. The police surgeon examined him and found on him the marks of numerous injections, arousing vigorous protests on the part of the patient because of the accusation of morphinism. In court, his personal physician testified that he had been treating K. for some time and that similar confusions had occurred previously, but to a milder degree, and that probably this episode was due to hypoglycemia with transitory psychotic manifestations. The case was dismissed when evidence of previous similar episodes was produced.

Several times, while on the trolley, the patient had overlooked his point of destination, being slightly confused, was picked up at the end of the line, and brought to a police station where the officers already familiar with his behavior called his wife to take him home. A month before his arrest, while visiting relatives, he began to make stupid and silly remarks, a symptom very familiar to his family as indicative of a reaction. He fought off the attempts of his family to give him some food, and finally had to be overpowered by several people so that a few pieces of sugar could be forced between his teeth. A year prior to his arrest he had had a severe hypoglycemic reaction, after erroneously taking a double dose of insulin (confusing U 20 with U 40 insulin, a mistake not noted then by his wife). At dinner he behaved normally at first, but then towards the end he became completely psychotic. He danced about the table and juggled oranges. Soon after, he lapsed into coma from which he could not be aroused by the oral administration of sugar, but required hospitalization and intravenous glucose therapy. The reaction of the patient to these attacks was one of embarrassment and chagrin. He constantly proclaimed his innocence and insisted that the statements and stupidities uttered during hypoglycemia were beyond his control; that he could not even remember them. In fact, he was aware of them only through information gathered from his family. These accidents upset him greatly, for he was ordinarily very polite and correct, and could not understand how he could have been so rude and discourteous.

*Case 2.* T., a 37-year-old manicurist, had been taking insulin a half hour before meals for three years. When for any reason the meal was delayed she displayed anxiety, nervousness, and a striking pallor. She became discourteous and impolite without being aware of it, and allegedly, because of this change, lost several customers. During an examination, her physician once noticed signs of hypoglycemia (tachycardia, sweating, pallor, etc.) and was struck by her rude behavior. She became abusive, in contrast to her usual demeanor, cursed and swore. All these symptoms disappeared promptly after sugar was supplied. On learning of her conduct, she was visibly disturbed and admitted that similar episodes had happened before.

One day, after taking her mid-day dose of 30 units of insulin at the house of a customer, she proceeded home for lunch. On the way she began to feel slightly "dizzy" and therefore quickened her pace in order to reach home sooner. She crossed a busy street against the traffic light whereupon the policeman shouted something to her (she could not recall what). Then he approached and questioned her. She cursed the officer, refused to divulge her identity and resisted arrest. She was taken by force to the police station as a "drunkard." In a short time she regained full consciousness, was quite amazed to find herself arrested, explained everything and identified herself. She was arraigned in court and held in jail for 24 hours for "misconduct and insulting an officer."

In addition to these cases, we had an experience with a juvenile diabetic who was arrested for misconduct on the street during hypoglycemia.

*Case 3.* G., a 15 year old student, diabetic since the age of nine, had had mild

hypoglycemic reactions with regular insulin, at home and at school, which were easily controlled. When protamine insulin was instituted, the lengthy forenoon sessions of high school gave rise to difficulties in management. His breakfast was taken at 7:30 a.m. following the injection of 40 units of protamine insulin. School lasted from 8:30 a.m. to 2 p.m., an interval of six and a half hours of intensive activity without the usual noon meal. Despite warnings to take a light snack at 11 a.m., the boy was too lazy or embarrassed to leave the classroom, and often risked hypoglycemia by not eating until he reached home at 3 o'clock.

One day, this carelessness resulted in the development of hypoglycemia while on the way home, when he became ataxic and confused, shouted and sang. Passing individuals deplored the sight of such a young "drunk." At this point, a police officer took him to the station house, not without difficulty because of the violent resistance exhibited by the patient. At the station house the police emptied his pockets and found the yellow card of the New York Diabetes Association identifying him as a diabetic patient taking insulin and giving directions for the administration of sugar in such instances. Naturally, with the usual prompt recovery after sugar, he was discharged. Since then he has been more diligent in observing the proper spacing of meals, and no further conflicts have arisen.

Recently widespread publicity was aroused when the defendant in a case of a traffic accident in Brooklyn, New York, pleaded that insulin hypoglycemia with the consequent loss of central control had led to the accident. The court censured him for driving a car when liable to such episodes, and held that the State should refuse to license those taking insulin. For a few days thereafter the local press carried considerable discussion regarding the justification of such a measure. The divergence of opinion and the confusion evident in some of the editorials indicate the need for clarification of this problem by competent legislation. It is now obvious that even more serious crimes may be committed during hypoglycemia. Robbery, arson, and homicide must be admitted as possibilities for consideration in the field of medical jurisprudence. From the experiences of some of our cases, it is conceivable that even sexual crimes may be the result of psychic changes during hypoglycemia.

#### MEDICO-LEGAL CRITERIA

Establishment of the hypoglycemic origin of any criminal action must be based on the following facts:

1. Naturally, the evidence must show that the person took insulin, and especially at a time conducive to the development of hypoglycemia when the criminal act was committed. Thus with regular insulin we admit maximum action usually within 3 to 6 hours. Beyond 8 to 10 hours insulin reaction could hardly be invoked as an alibi. With protamine insulin the action is considerably prolonged and hypoglycemic accidents may occur even after 24 hours. Therefore, the increasing use of protamine insulin will complicate the medico-legal aspect of such incidents all the more, and proof of hypoglycemia will require chemical determination of the blood sugar level.

2. Evidence of hypoglycemia by clinical and chemical methods. The association of the well known somatic changes of hypoglycemia will tend to substantiate the diagnosis, and chemical corroboration will prove it. As to the latter, it is obvious that the tests should be done by a competent chemist, and an accepted standard method of analysis used.

3. The history of a contributory factor to the development of hypoglycemia is of importance, such as undue exertion or excitement, the omission of a meal or reduction of carbohydrate in the meal, or unusual delay in eating after the injection. However, we must admit that even without any such obvious reasons hypoglycemic reactions may develop in well controlled diabetics.

4. The history of any mental changes during previous hypoglycemic episodes, and particularly psychic manifestations resembling those leading to the legal difficulty in question.

5. The evidence that the actions during hypoglycemia stand in sharp contrast to the normal behavior of the involved person, as illustrated in all the above examples.

6. The presence of a partial or complete amnesia for the incidents in question. It is acknowledged that this is one of the most characteristic features of the hypoglycemic state, particularly when severe. The amnesia is most profound immediately following the reaction and later tends to clear up partially. This may be attributed in part to the tendency and ability of the patient to reconstruct the sequence of events from the conversation of witnesses. When confronted with the story of his actions, the hypoglycemic individual will display such a dramatic reaction of surprise and shame that this feature may distinguish real amnesia from a simulated one.

7. The prompt restoration of the normal personality with the administration of carbohydrate. This is, so to say, a therapeutic test.

As yet, no provocative test has been established which will precipitate a reaction for the purpose of observation by physicians or public officials. An obvious method would be the administration of an overdosage of insulin. In view of the rôle of cerebral anoxemia in the etiology of hypoglycemic reactions, perhaps as in aviation, tests under reduced oxygen tension may distinguish those diabetic individuals particularly susceptible to severe mental reactions.

When legal conflicts arise in such cases where hypoglycemia is proved, then the mental changes associated with this state are, we believe, sufficient grounds to consider the individual not responsible for his actions at such a time. This principle should be established and recognized by appropriate legislation. Of course, abuse of such laws by diabetic criminals will have to be considered, but careful medical analysis of each case should obviate such difficulties.

## LEGAL AND SOCIOLOGICAL ASPECTS

Having demonstrated the problems involving criminal law it is important to consider certain questions of civil law. It should be established that these patients are legally irresponsible during hypoglycemia. Thus, contracts and wills drawn up when the party is in a hypoglycemic state should be held invalid. Civil suits for libel and slander against diabetics should take into account the possibility of hypoglycemia. Divorce and breach of promise suits must be considered with this view in mind.

In addition, the question of licensure for different occupations involving public safety must be discussed. It is obvious that a diabetic, subject to severe hypoglycemic reactions, is unfit to drive a car, bus, locomotive, or airplane. A hypoglycemic reaction in one of these occupations may endanger not only the life of the diabetic driver but many innocent persons. Similarly, a reaction in a railroad switchman, traffic policeman, or lighthouse tender can cause untold damage to the unsuspecting public. According to various statisticians there are in this country more deaths from accidents than from all the contagious and infectious diseases combined, except tuberculosis. In view of the appalling death toll from this cause, an attempt must be made to weed out such individuals from all hazardous occupations. Stricter license tests would eliminate many drivers who are physically or mentally unfit. In this category must be included those diabetics who tend to develop frequent hypoglycemic reactions.

In the absence of adequate legislation, the physician as always must continue to be teacher and sociologist to his patients. He must urge a change or restriction of occupation when indicated, limitation of previous activities must be outlined, etc. We are familiar with the case of a surgeon who voluntarily restricted his professional activities to minor surgery, for fear of hypoglycemic reactions during major abdominal operations, which naturally required more time and exertion. Another physician gave up general practice for an administrative hospital position because the irregularities of his daily life were conducive to hypoglycemic reactions. The physician must caution those patients particularly susceptible to hypoglycemia against driving a car, working in critical occupations such as construction work, and indulging in strenuous sports, including mountain climbing and swimming. These patients should choose occupations of a sedentary nature, or at least indoor positions where they may be better protected against accidents and in which they are less apt to be a source of danger to innocent bystanders. This problem is of particular importance in the juvenile diabetics for whom vocational guidance must be intelligently applied, the children being trained in fields other than those which may expose them to undue hazard during hypoglycemic episodes.



## SUMMARY

In recent years hypoglycemic reactions have received wide medical attention. There are two groups with this syndrome:

1. Those with spontaneous hypoglycemia, either "idiopathic" or due to endocrine disturbances, and
2. Those diabetic individuals taking insulin.

It is interesting to note the accumulation of a voluminous literature on spontaneous hypoglycemia and its manifestations whereas the obviously more frequent hypoglycemia in diabetes has failed to arouse such interest. Although the absolute incidence of insulin reactions is greater than the literature would indicate, in the light of the innumerable insulin injections taken daily throughout the world it is relatively infrequent.

This report is concerned mainly with the mental changes of hypoglycemic diabetics because of the medico-legal importance of accidents arising from this state. From the mildest symptoms of anxiety and irritability to complete confusion and disorientation, the wide range of mental reactions has been presented and illustrated. An attempt at classification into mild, moderate, and severe cases has been made. The possibilities of legal conflicts arising from the somatic and mental changes of the hypoglycemic state have been emphasized and the need for appropriate legislative recognition of this problem has been stressed. The question of licensure for auto drivers, engineers, aviators, etc. has been discussed. Medico-legal criteria for actions committed during hypoglycemia have been established. The difficult and delicate sociological problems involved in each patient susceptible to mental changes during hypoglycemia have been outlined.

Until there is public recognition and appreciation of the legal and social aspects of these diabetic individuals the physician must continue his three-fold rôle of guide, teacher, and sociologist. He will have to educate the family, friends, and business associates of each patient as to the true nature of the personality changes during hypoglycemia. He must assist social agencies in adapting the patient to the necessarily altered circumstances of life.

The difficulties described should not stigmatize the diabetic patient as an inferior in our highly competitive society. It should be stated that the overwhelming majority of diabetics are capable of becoming an integral part of society, suffering no appreciable handicap, but on the contrary successfully fulfilling their obligations in all fields of human endeavor.

## CONCLUSIONS

1. Diabetic individuals, taking insulin, may present in hypoglycemia a wide variety of behavioristic and mental changes foreign to their normal personality.

2. Because of the somatic and mental changes manifest during hypoglycemia, actions may be committed which provoke conflicts with law and society.

3. Some uniform legislative procedure should be established to deal with such incidents.

4. The physician must continue to be guide, teacher, and sociologist to these patients who must adapt themselves to an altered life.

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# SPECIFIC SEROTHERAPY AND CHEMOTHERAPY OF THE PNEUMOCOCCUS PNEUMONIAS \*

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ADVANCES in the therapy of pneumonia have been occurring in recent years at an ever-accelerating pace. Nearly three decades elapsed from the earliest recognition of the etiological relationship of the pneumococcus to pneumonia in man and its first successful therapeutic application in specific serum treatment. This first step in the specific therapy of pneumonia was made possible through the subdivision of pneumococci into specific types. Therapy then became available for the most common of these types, namely, Type I. From the earliest use of specific antipneumococcus horse serums in the treatment of pneumococcus Type I pneumonia, it was recognized that, to be most effective, it was necessary to have potent type-specific serums, to give these serums intravenously in adequate amounts, and to use them early in the disease. Although constantly favorable results have been reported from individual clinics, this therapy did not receive widespread use because the treatment was cumbersome, the diagnostic procedures difficult and time-consuming, the available serums were of low potency, and the effect on the total fatality rate was so slight that it did not seem to justify the extensive use of the treatment.

*Concentrated Serums.* The introduction of methods for refining and concentrating the effective antibody contained in antipneumococcus horse serums and the gradual elimination from the concentrated antibodies of most of the substances responsible for the untoward reactions simplified the treatment and made possible an extension of the use of serum to include most patients with Type I and Type II pneumococcus pneumonias. The beneficial results of treatment in cases of Type I pneumonia became readily apparent with the use of these serums, but the results in cases of Type II pneumonia varied considerably, due in large measure to the low potency of the serums available for this type, even after concentration, and the inadequate dosage used.

*New Types of Pneumococci.* The classification of pneumococci formerly included in Group IV into the specific types IV to XXXII was the next great advance. With this new classification, strains formerly recognized by their atypical reaction with Types II and III serums were identified as the important specific Types V and VIII, respectively. When it became

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possible to identify the type of each pneumococcus regardless of its source, it was found that the new types varied considerably in the frequency with which they caused pneumonia or other infections, and also in the frequency with which they occurred as normal inhabitants of the respiratory tract in man. Most important, from the practical point of view, was the fact that a small number of these types was found to account for a considerable proportion of the cases of severe pneumonia, and for these common types, notably Types V, VII and VIII, therapeutic serums were prepared which were of high potency and were soon shown to be effective therapeutically.

With the aid of the new classification, it was also found that the types of pneumococci responsible for the majority of cases of pneumonia in infants and children were different from the types most frequent in the pneumonias of adults. Types XIV, VI and XIX were found to be the predominant types in the pneumonias of infants. It also became apparent that multiple types of pneumococci could be found in persons acutely ill with respiratory infections. Further experience permitted a practical interpretation of such findings which minimized the difficulties they presented. Certain types, notably Types I, II and V in adults and Types XIV, I and V in infants and children have been found quite consistently to bear an etiological relation to acute pulmonary infection. Other types, such as III, VII and VIII in adults and VI and XIX in infants, while etiologically related to many cases of acute pneumonia, have also been found frequently to be normal inhabitants of the nasopharynx without relation to acute disease. Still others, such as Types X, XX, and the types beyond XX, can usually be considered as part of the normal pharyngeal flora and only rarely give rise to acute pneumonia.

*Classification of Pneumonias.* With the extension of the use of specific serums to the newer types of pneumococci, it became more apparent than previously that the older classification of pneumonias into clinical anatomical entities, such as lobar pneumonia and bronchopneumonia, was no longer of any great significance. Many severe atypical pneumonias were found to be caused by common types of pneumococci. The etiological classification became the important one from the point of view of prognosis and therapy.

*Improvements in Typing.* Coincident with the developments and improvements in serum production and the extension of treatment to include the newer types, there were important advances made in the diagnostic procedures essential to the proper use of specific serums. The earlier methods of typing pneumococci usually involved waiting for the death of a mouse or sacrificing the animal injected with sputum after an interval of eight to 24 hours. The peritoneal exudate after that time frequently showed atypical or cross agglutinations. Errors were inevitable, valuable time was lost, and the efficacy of treatment reduced. The introduction of the Sabin microscopic method of agglutination from the peritoneal exudate of a mouse made possible more accurate type diagnosis within a period of three to six hours after a proper specimen of sputum was obtained. More recently the introduction of the Neufeld technic made possible type diagnosis directly from

sputum in about three-fourths of all cases within a matter of a few minutes of the time that a good specimen from a case of pneumococcal pneumonia arrives at a properly equipped laboratory. In specimens of sputum in which the pneumococci are rare, the application of this method to the peritoneal exudate, withdrawn three to five hours after a mouse is injected with the sputum, makes possible a type diagnosis in almost every instance. In cases in which sputum is not available, notably in infants and children, throat swabs incubated in proper media \* may be typed by this method directly after four to six hours, or the growth may be injected into a mouse in the same manner as sputum. This method of typing is also applicable to blood cultures. In such cultures, as soon as growth is recognized by the earliest color change, the type can be identified within a few minutes directly by this method.

*Rabbit Serums.* Within the past two years, antipneumococcus rabbit serums have been introduced into the therapy of pneumonia and have considerably broadened the scope of specific therapy and increased its efficacy. Experimentally many differences had been observed between antipneumococcus serums produced in horses and in rabbits. A number of them were considered to be of possible importance in therapy. While most of these advantages are theoretical, there are a number of practical considerations which make therapeutic rabbit serums an important contribution. (1) It is possible to produce effective serums more rapidly in rabbits than in horses, and these can be used with safety in the treatment of human cases. (2) For most types the titers of antibody are uniformly higher in rabbits than in horses. It thus becomes possible to give more effective doses in smaller volumes, and less time is lost. (3) It is more economical to produce serums for the less frequent types in the smaller animal. (4) The size of the antibody molecule has been found to be smaller in antipneumococcus rabbit serums than in horse serums of the same types (at least this has been shown for Types I and III). This offers the possibility of more effective penetration of the rabbit antibody into infected tissues and exudates. (5) It is possible to treat with rabbit serums patients who are specifically sensitive to horse serums, particularly those who have previously received horse serum injections, and many allergic reactions are thus avoided. Perhaps most important is the fact that for two of the most frequent types, namely, Types II and VIII, serums produced in horses have been of low potency, and in rabbits considerably higher concentrations of specific antibody for these types can be achieved. For Types I, V and VII, most horse serums have been fairly uniformly high in concentration and correspondingly efficacious.

In the use of Type XIV antipneumococcus horse serums an unusual number of reactions was observed, some of them serious and even fatal. It was found that serums of horses immunized with Type XIV pneumococcus have

\* Rabbit blood broth or serum broth may be used. Human ascitic fluid from nephrotic children has been found to be a favorable medium for this purpose at the Children's Hospital in Boston.

the property of agglutinating human erythrocytes of all blood groups. Anti-pneumococcus Type XIV rabbit serums were found not to have this property and are devoid of untoward reactions; thus they can be used safely. Nor were horse or rabbit serums for any of the other known types found to exhibit this unusual property.\*

*Standardization of Serums.* Advances have also been made in the standardization of serums. The earlier unconcentrated serums varied in potency as much as 100-fold or even more. The use of standard serums in the titration of the therapeutic products has introduced greater uniformity in the potency of the specific antibodies. The estimation of dosage with these standardized serums has been somewhat simplified.

*Sulfanilamide.* The widespread use of the newer chemotherapeutic agents, notably sulfanilamide, in various bacterial infections and the bacteriostatic effect of this drug on certain types of pneumococci in vitro have suggested the possibility that it might have some field of usefulness in the treatment of cases of pneumococcic pneumonia. Furthermore, the experimental evidence that sulfanilamide, in combination with specific serums, was more effective than either the drug or specific serum alone suggested the possibility that this combination might be a more effective method of treatment in certain cases of pneumococcic pneumonia where specific serums alone have not been found to be very effective. The high death rate from Type III pneumococcal infection and the relatively low potency of specific antibodies produced in both horses and rabbits for this type suggested the therapeutic application of the combined rabbit serum and sulfanilamide treatment in cases of pneumococcus Type III pneumonia. There appeared some evidence that sulfanilamide itself had beneficial effects on the course of such cases,<sup>1, 2</sup> and our own studies<sup>3</sup> indicated that its use in combination with serum is definitely superior to its use alone.

For other types of pneumococcus pneumonia, no clear evidence of the efficacy of this drug has been available until very recently when there has appeared a study indicating that it may have therapeutic value in some cases.<sup>4</sup>

*Sulfapyridine.* Recently sulfapyridine has been introduced into the therapy of pneumonia in Great Britain, and a number of reports have appeared in the British<sup>5</sup> and American literature<sup>6</sup> concerning the efficacy of this agent in the treatment of pneumococcic pneumonias. Striking results are reported in the treatment of infants and children, and reductions in death rate and beneficial clinical effects are also being reported in adults.

#### RESULTS OF SPECIFIC SERUM TREATMENT

At the Boston City Hospital we have tried to keep pace with these various developments. We have recently summarized the results of specific serum therapy in the treatment of pneumococcus pneumonia of Types I, II, III, V

\* FINLAND, M., and CURNEN, E. C.: Agglutinins for human erythrocytes in Type XIV antipneumococcic horse serums, *Science*, 1938, lxxxvii, 417-418.

and VII up to July 1938.<sup>7</sup> The early serums that we had available were experimental lots of low potency and produced reactions of varying severity in moderate numbers of cases. The more recent lots have been relatively free of untoward reactions and much higher in potency. This is particularly true of the recent therapeutic rabbit serums that we have had available for almost all types of pneumococci. The supply of the newer serums was also limited and their use was necessarily restricted to the severer cases or to early cases in order that some evidence of efficacy could be more readily acquired. As a greater supply of serums became available, a larger percentage of cases, particularly of the common types, were treated with serum, omitting only those cases that showed evidence of recovery or that had already died at the time the type was determined. In our compilations we have included all cases receiving the various therapeutic agents under consideration, regardless of the condition of the patient at the time of treatment and regardless of any complicating factors. We feel that this is of the utmost importance, since exclusion of some fatal cases is open to the interpretation that the therapy played some part in the outcome of the cases excluded. It is our feeling that such patients should be included and the deaths explained, since these cases form an integral part of the clinical disease which we are treating and since it is important to know under which conditions the various therapeutic agents are not effective or might possibly be harmful.

*Type I.* We may summarize briefly the results of specific serum therapy in the more common types of pneumococcus pneumonia up to the beginning of this season. In Type I pneumococcus pneumonia <sup>7a</sup> the percentage of cases included for treatment with serum increased during the last three years from 43 to 89 per cent. The mortality for all the serum treated cases has remained about 19 per cent, as compared to a 40 per cent mortality in the contemporaneous non-serum treated cases and in the non-serum treated cases for several previous years. The best results were obtained when treatment was started early so that in cases treated before the end of the fourth day the mortality for all cases was 13 per cent and for bacteremic cases 28 per cent. The severity of the entire group of cases is indicated by the fact that about 40 per cent of all of the cases chosen for treatment had blood stream invasion at the time treatment was begun. In this type, as in the others that we shall mention, all of the fatal treated cases are included in the calculation of the death rate. In most instances there were definite factors aside from the pneumonia contributing to the deaths. In a number of them the treatment was applied late and death occurred shortly after the beginning of therapy, and in others, death was due to complications either of the infection or not associated with the infection. It is possible, by exclusion of cases in which the treatment was obviously inadequate or where other factors contributed to mortality, to indicate a death rate in serum treated Type I cases as low as 3 per cent. This is more or less true for

most of the other types which we have had an opportunity to treat adequately with good specific serums.

*Type II.* In the Type II cases <sup>7b</sup> our results have varied during certain years and the poor results were attributed to inadequate therapy in terms of units of antibody per patient. During the past three years the percentage of Type II cases that we have included for specific serum therapy has increased from 33 to 82 per cent, and the mortality averaged 19 per cent among the 148 cases treated during this period. Among 121 consecutive cases treated before the end of the fourth day the mortality was 14 per cent in all cases and 27 per cent in the bacteremic cases. This compares with a 36 per cent death rate in contemporaneous non-serum treated Type II cases and, over a nine year period, a death rate of 40 per cent in all cases and 76 per cent in bacteremic cases. In this type also the severity of the cases as a group is indicated by the fact that 40 per cent of the cases included for serum treatment were bacteremic cases. Since it has been repeatedly shown that the institution of serum therapy prevents the occurrence of bacteremia in patients in whom such invasion has not yet occurred at the time treatment is begun, this percentage of bacteremic cases is more significant than if it were found in non-serum treated cases. In a small series of cases treated with rabbit serums during the last year of this study, the results were even more striking than those previously demonstrated with horse serums.

*Types V and VII.* In the cases of Types V and VII pneumococcus pneumonia <sup>7a</sup> the reduction in death rate has been greater than in either of the two commoner types, I and II. This has been especially true for Type V pneumococcus pneumonias which at the Boston City Hospital have been associated regularly with a high mortality (40 per cent) and a high bacteremic incidence before specific serums for this type became available. This figure for mortality is somewhat higher than that reported from other clinics, which is usually given as about 25 per cent. In the 81 cases of Type V pneumococcus pneumonia treated with specific serum before July 1, 1938 (almost all of these were treated with horse serums), there were only eight deaths, or 10 per cent; and 33 per cent of the cases were bacteremic. The non-serum treated case fatality rate for the previous nine year period was 41 per cent with a 43 per cent bacteremic incidence. Prior to July 1, 1938, there were 79 cases of Type VII pneumococcus pneumonia treated with serum with nine deaths, a mortality rate of 12 per cent. This compared with an average contemporaneous and previous mortality rate of 29 per cent in 160 cases not treated with serum. Twenty per cent of the Type VII treated cases were bacteremic as compared with 24 per cent of the non-serum treated cases of this type. When treatment was begun before the end of the *fifth* day of illness, the death rate was 7 per cent among the Type V cases and 3 per cent in the Type VII cases.

*Type VIII.* The results in our cases of pneumococcus Type VIII pneumonia have not yet been reported in detail. During the first season that serums for this type became available, they were produced in horses, were



of low potency, and frequently gave reactions of moderate severity. Of 11 cases treated with such serums there were four deaths. Although only the sickest patients were chosen for treatment and the dose of antibody used was grossly inadequate, these results can be considered definitely poor. During the following year rabbit serums were available for most of the cases and were of higher potency than the horse serums, and both the rabbit and horse serums were considerably freer of reactions. During that year 30 cases were treated with three deaths, the latter occurring in hopeless cases. The average death rate for cases of pneumonia due to this type during the past 10 years has been about 25 per cent.

These figures, although indicating a definite and marked reduction in death rate as a result of specific serum therapy, do not reflect the entire picture. In the first place, the clinical response to this treatment has been striking. In pneumonia of these five types treated with serum, in about 80 per cent of the cases a clinical crisis has been induced within eight to 36 hours of the beginning of treatment. We have already called attention to the fact that there have been important factors contributing to the failures in the Type I cases, leaving only a small residual where the specific treatment could be said to be ineffective. The same was true for the other types.

*Type III.* We have recently reviewed the results of treatment in cases of Type III pneumococcus pneumonia treated with sulfanilamide or specific serum or with a combination of these two agents.<sup>7c</sup> The results, as reflected in the death rate, were not very striking, but there was definite evidence from an analysis of the clinical results in these cases and from bacteriological and immunological studies<sup>3</sup> that the pneumococcal infection was definitely benefited.

*Higher Types.* Serums for a number of the higher types became available during the last two years. As in the more common types, the supply available at first was limited and only the most severely ill patients were chosen for treatment. During the present season, however, we have had available a supply of horse and rabbit serums of high potency for a number of types and have treated a small group of patients with results that have been similar to those previously observed with the more common types, as we shall note later.

*Sulfanilamide.* We have not made any systematic study of the use of sulfanilamide except in the cases of Type III pneumonias already mentioned. We have used this drug in conjunction with specific serum in some of the severer or complicated cases of pneumonias due to the commoner types, and alone in a number of cases due to the higher types when specific serums were not available. In the pneumonias due to the common types<sup>7</sup> sulfanilamide was continued in those cases in which treatment with the drug was begun before typing was obtained, when the patients were seemingly benefited. In most instances, however, specific serums were given to cases of these types because the clinical condition of the patient had not shown adequate improvement with the drug. The number of cases treated with

sulfanilamide alone are too few to warrant any conclusions. In general, the clinical results were not striking. Nor was there any sharp reduction in death rate noted over previous years. Among 43 cases treated, there were 16 deaths (37 per cent). Six of the deaths were among the 11 bacteremic patients. It is interesting to note that three of the bacteremic cases that recovered after sulfanilamide therapy had Type XII pneumococcal pneumonia. In most of the patients who recovered following treatment with sulfanilamide, the termination of the acute illness did not seem to be in relation to the therapy.

#### RECENT RESULTS OF TREATMENT WITH SULFAPYRIDINE AND SERUM USED ALONE OR IN COMBINATION

Probably the greatest interest at the moment concerns the results obtained during the present season with the use of sulfapyridine alone or in combination with specific serums. Since early this fall we have used this drug in the treatment of 175 adult patients with pneumonia due to specific types of pneumococci. Eighty of these patients received specific serums in addition. Since July 1, 1938, we have also treated 167 cases with specific serums alone. The three groups of patients are not entirely comparable. It was natural, having available specific agents of known efficacy, that only milder cases were first chosen for treatment with the drug alone. This is reflected in the relatively low bacteremic rates as compared with the groups of patients treated with serum alone. Likewise, inasmuch as experimental evidence pointed towards a greater efficacy of the drug when used in combination with specific serums, it was natural that this treatment was chosen for the more severe cases, namely, the bacteremic patients, particularly those in the older age groups.

*Mortality in Relation to Age and Bacteremia.* The distribution of cases according to type of treatment received, the age, and the results of blood culture are shown in table 1. In the 167 cases treated with serum alone there was the usual incidence of bacteremia, averaging 27 per cent,\* and, as usual, bacteremia was more frequent in the older age groups. The death rate in this group of cases was 13 per cent. Among the cases treated with sulfapyridine alone, the bacteremic incidence was only 17 per cent, and in the older patients the relatively infrequent occurrence of bacteremia indicates that we were dealing with a definitely milder group of patients over 60 years of age. For the entire group of 95 patients, the death rate was 15 per cent. This probably indicates a definite reduction in fatality rate over that which might be expected in patients not treated with specific serums or chemicals. Considering the relative bacteremic incidence, however, these results may be considered as probably inferior to those obtained with serum alone.

\* All bacteremic rates refer to the results of blood cultures before the institution of therapy.

TABLE I

Cases of Pneumococcic Pneumonia Treated at the Boston City Hospital  
July 1, 1938 to March 15, 1939

Age Group	Bacteremic		Non-Bacteremic		All Cases			Per Cent Bacteremic
	Number	Died	Number	Died	Number	Died	Per Cent Died	
Cases Treated with Serum Alone:								
12-19	8	1	24	0	32	1	3	25
20-39	15	2	56	2	71	4	6	21
40-59	17	9	36	3	53	12	23	32
60+	5	3	6	1	11	4	36	45
All	45	15	122	6	167	21	13	27
	33% Died		5% Died					
Case Treated with Sulfapyridine Alone:								
12-19	—	—	14	1	14	1	7	0
20-39	4	0	23	2	27	2	7	15
40-59	9	3	24	1	33	4	12	27
60+	3	3	18	4	21	7	33	14
All	16	6	79	8	95	14	15	17
	38% Died		10% Died					
Cases Treated with Specific Serum and Sulfapyridine:								
12-19	1	1	—	—	1	1	—	—
20-39	6	1	8	0	14	1	7	43
40-59	17	9	21	4	38	13	34	45
60+	16	5	11	1	27	6	22	59
All	40	16	40	5	80	21	26	50
	40% Died		13% Died					

The group of 80 patients chosen for treatment with the combination of sulfapyridine and serum contained a greater proportion of older patients and the *incidence of bacteremia was about twice that in the patients treated with serum alone and three times that in the cases treated with sulfapyridine alone.* It is to be expected that the fatality rate in such a group of patients would be considerably greater than in the first two groups. The total bacteremic incidence in this group was 50 per cent. Eighty-one per cent of these patients were over the age of 40, and 34 per cent were over 60 years of age. Among the 27 patients over 60, 16 or 59 per cent were bacteremic.

Nevertheless, in this latter group the mortality rate was only 22 per cent. In similar cases treated without specific serums or drugs we have found, over a number of years, that the expected fatality rate in this age group with this bacteremic incidence is between 75 and 90 per cent. With specific serums alone, it is 50 to 60 per cent.<sup>7, 8</sup>

*Results in Different Types.* The number of cases of each type are too few to consider in detail. The results for each of the common types and for all the higher types are shown in table 2. Two interesting features may be pointed out. Of 14 Type I cases over 60 years old and treated with serum and sulfapyridine, 12 were bacteremic and only 4 died. Among the cases

TABLE II  
Pneumococcic Pneumonias Arranged by Type

Type	Serum Alone*				Sulfapyridine Alone				Serum and Sulfapyridine			
	All Cases		Bacteremic Cases		All Cases		Bacteremic Cases		All Cases		Bacteremic Cases	
	Number	Died	Number	Died	Number	Died	Number	Died	Number	Died	Number	Died
I	50 <sup>5</sup>	4 <sup>1</sup>	13 <sup>1</sup>	3 <sup>1</sup>	33	3	9	2	33	8	19	6
II	24 <sup>1</sup>	6 <sup>1</sup>	8 <sup>1</sup>	3 <sup>1</sup>	2	0	0	0	17	4	10	4
III	9 <sup>5</sup>	2 <sup>1</sup>	2 <sup>1</sup>	2 <sup>1</sup>	26	4	4	2	16	3	2	2
V	18 <sup>4</sup>	3 <sup>1</sup>	4	2	6	1	1	1	4	1	3	1
VII	20 <sup>2</sup>	3 <sup>1</sup>	4 <sup>1</sup>	2 <sup>1</sup>	6	0	0	—	3	0	1	0
VIII	18	1	6	1	6	0	1	0	3	2	1	0
Other Specific Types	28 <sup>3</sup>	2	8	2	16	6	1	1	4	3	4	3
All Types	167 <sup>20</sup>	21 <sup>5</sup>	45 <sup>4</sup>	15 <sup>4</sup>	95	14	16	6	80	21	40	16
Per Cent Died	13		33		15		38		26		40	

\* Includes patients who received sulfanilamide in addition. The numbers are shown by superscripts

due to types other than I, II, III, V, VII and VIII there were five deaths in the 32 cases that received serum, including the four cases treated with sulfapyridine in addition. These 32 cases included 13 with bacteremia and 16 over 40 years of age. It is worth mentioning here that all five of these fatal cases had important factors other than the pneumococcic pneumonia which contributed to the fatal outcome. It may also be noted that the only two bacteremic cases of Type III pneumonia who recovered were treated with sulfapyridine alone. We have previously noted three recoveries in bacteremic cases of this type treated with sulfanilamide alone.<sup>70</sup>

The present results are, therefore, most encouraging. It is obvious that it will be necessary to have a considerably larger number of cases in each

category before final conclusions can be reached as to the relative efficacy of the drug and serum alone or in combination. From the practical point of view, it is evident that *both specific serums and sulfapyridine are effective agents*, and that in severe cases the use of the combination of the drug and specific serum has shown definite effects in reducing the fatality in the severest group of patients in which the mortality is the highest.

*Clinical Response.* From the point of view of the clinical response, our experience has led us to expect that when good type-specific serums are given in adequate amounts a rapid deffervescence of the symptoms of acute disease takes place within six to 24 hours in the great majority of the patients, and they look and feel completely relieved of symptoms. With the use of sulfapyridine alone, the patients manifest evidence of illness for a considerably longer period, and this is particularly true in the patients with the severer illness associated with bacteremia. Furthermore, the possible antipyretic as well as the toxic effects of this drug make the proper evaluation of the course of the disease difficult. We have found that the use of the drug alone, in all but the mildest cases, must be continued for a minimum of 48 to 72 hours or even longer after the deffervescence of fever. In patients treated with a combination of serum and sulfapyridine, if adequate doses of both are used, the drug can be dispensed with in periods varying from 12 to 36 hours after the initial dose, and probably much smaller doses of serum are necessary than when the drug is not used. It has, therefore, been a great comfort to see severely ill patients whose prognosis is extremely poor manifest evidence of complete recovery within a few hours after the beginning of therapy with drug and serum.

It is not possible at this time to present a detailed account of the dosage used in various cases, the results of the estimations of the blood concentrations, and the toxic effects observed. In general, we have used doses similar to those employed by others. We have noted variations in absorption and in the toxic effects. In a number of mild cases, rapid recovery has occurred when it was obvious that practically no absorption of the drug took place, as evidenced by the low or even undetectable concentrations attained in the blood. Such cases make the evaluation of the data difficult until a large number of cases are available for analysis of all the factors entering into mortality as well as the evaluation of the clinical course under different types of therapy.

*Untoward Effects.* As to toxic effects, we have noted most of the untoward symptoms already noted by others. Nausea was most prominent and occurred in about two-thirds of the cases. In about one-half of those with nausea there was vomiting, which varied in severity, and in about one-half of the latter this symptom was severe enough to interfere with further oral administration of the drug. Intravenous injections of saline and glucose were found to be of only slight help in some, but not all such cases. Moderate anemia has occurred early in a number of cases but the progressive type of anemia noted with sulfanilamide has not been noted

frequently, presumably because the drug has usually been discontinued after a shorter period. Cyanosis was less frequent and less marked than with sulfanilamide. One fatal case of agranulocytosis was observed in a 19 year old boy not included in the above tables since no pneumococcus type was obtained in his sputum, the causative agent being a staphylococcus. In this patient there was total absence of granulocytes in the blood 36 hours after onset of therapy and death occurred 12 hours later. Severe mental and physical depression and, in some cases, marked excitement have been noted during the administration of this drug, even when the infection has apparently improved. Impaired renal function is one of the important complications which we have noted, although the evidence to implicate the drug is not complete. In one case there was nitrogen retention and edema, and in a second, nitrogen retention and mental and motor manifestations of uremia. In these two cases the evidence of renal impairment occurred after the patient had been on treatment for more than four days and after the acute infection had obviously subsided, and when the pulmonary lesion showed evidence of clearing or had completely cleared. Both these patients died. Neither had received serum.

A number of cases have already been encountered in which, after treatment with sulfapyridine alone, relapse of the pneumonia occurred in the same or other portions of the lung. The same or other types of pneumococci or other organisms, notably hemolytic streptococci, were recovered during the relapse. Such relapses have occurred three to 10 or more days after complete subsidence of fever and after what was considered to be an adequate dose of the drug.

Our experience is as yet too limited to permit a detailed discussion of both the beneficial results and the failures of treatment with sulfapyridine. The failures of specific treatment and its limitations have been adequately discussed on many occasions, and the circumstances under which this treatment alone is most effective have been detailed. The introduction of rabbit serums has widened the scope of effectiveness of these specific serums. Similar studies in adequate numbers of cases treated with sulfapyridine alone and with a combination of sulfapyridine and serum will need to be carried out and analyzed in great detail before the complete scope of usefulness and the limitations of the drug alone or in combination with serum and the relative efficiency of these various types of treatment can be evaluated. Furthermore, the results must be assessed for each of the specific pneumococcus types.

In the meantime, we feel that in the therapy of the pneumococcus pneumonias, we now have two very effective agents—specific serum and sulfapyridine. The abandonment of specific serum in favor of the drug alone would be unfortunate at this time. For the present, and until more data become available, we feel that the following procedures represent the method of choice for the treatment of patients with acute pneumonia:

(1) Each case should have adequate bacteriological control, including sputum examination with smear, culture, and typing, and a blood culture should be made *before any serum or drug is administered*. It is to be borne in mind that negative blood cultures taken after treatment with either serum or drugs like sulfanilamide or sulfapyridine give a false sense of security and are not of the same prognostic significance as positive blood cultures obtained before such treatment is instituted. After any serum therapy there is frequently a transient sterilization of the blood stream for six to 24 hours. If an adequate dose of specific antibody has been given, the blood remains free of bacteria unless focal complications already exist. After sulfanilamide or sulfapyridine has been given, the bacteriostatic effect of the drug may serve to prevent the growth of small or moderate numbers of bacteria which may be present in the blood.

(2) Complete blood counts should be made, urine analysis should be done, and blood non-protein nitrogen determined before treatment and frequently thereafter when sulfapyridine is used.

(3) Treatment with sulfapyridine may be started in all cases as soon as the diagnosis of pneumonia is established. It is recommended that patients with polynuclear neutropenia should not be treated with this drug until more information becomes available to indicate that treatment of such patients with this drug is safe. Leukopenia with a high percentage of polynuclear leukocytes is probably not a contra-indication to the use of the drug. Likewise, until it is definitely shown that patients with jaundice or with known or suspected liver or renal disease can tolerate this drug, it is probably wise to avoid treating such cases with sulfapyridine.

(4) In adult patients over 40 years of age and in all pregnant or recently parturient women in whom any of the common types of pneumococci are found, and in all cases in which the blood culture yields specific types of pneumococci, specific serums should be given as soon as possible to insure the most effective therapeutic response unless, at the time when the results of the blood culture or typing are available, there is already definite evidence that the acute disease has subsided. Treatment with adequate amounts of serum helps to insure complete and rapid recovery without recrudescence.

In the choice of specific serums for therapy, it may be said that uniformly beneficial results are obtained only when highly potent serums free of any but the milder reactions are used in adequate amounts, and that when serums of low potency are given in relatively small doses and result in frequent and severe reactions the beneficial effects of the serums are greatly reduced. It is our feeling that the wide variations in results obtained with specific serums can be explained in large measure on this basis.

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# RECENT ADVANCES IN THE TREATMENT OF PELLAGRA AND ASSOCIATED DEFICIENCIES \*

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IN 1735 Gaspar Casal, a Spanish physician, first described pellagra and shrewdly pointed out that this disease is related to an inadequate diet.<sup>1</sup> That diet was the controlling factor in the etiology of the disease was not suggested again until the work of Goldberger, Waring and Willets<sup>2</sup> in 1915. During the next two decades, the full significance of diet in the development of pellagra gradually became evident because of the frequent association of the disease with faulty nutrition. Later, the administration of a high caloric diet, rich in protein and vitamins, supplemented with large amounts of antipellagic materials such as yeast, wheat germ or liver extract, became the accepted form of therapy.<sup>3, 4, 5</sup> Although beneficial in most cases, this treatment is often impractical. It frequently necessitates hospitalization of the severely ill patients for several weeks, during which time almost constant supervision by a physician, nurse or dietitian is required. Furthermore, many of the patients who improve following this therapy are unable to buy, after discharge from the hospital, the relatively expensive foods which will protect them against recurrences of the disease. In addition, failure to recognize pellagra in its subclinical or mild form continued to be an obstacle to effective and lasting treatment, as advanced pellagra often developed before a diagnosis was made and therapy instituted. It is not surprising, therefore, that efforts have been directed toward obtaining a more practical form of treatment, toward developing methods by which an earlier diagnosis can be made, and toward identifying and isolating the anti-pellagic factors.

A little more than a year ago, Elvehjem, Madden, Strong and Woolley<sup>6</sup> reported that nicotinic acid and nicotinic acid amide are effective in curing blacktongue in dogs, a canine disease considered by many investigators to be an analogue of human pellagra. These observations suggested the possible therapeutic value of these compounds in pellagra and stimulated many investigators to study their effectiveness in treating this disease. As a result of the dramatic improvement of several symptoms of the disease reported by all workers in the field,<sup>7-19</sup> nicotinic acid became an accepted part of pellagra therapy. Its discovery has made possible great advances not

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only in the treatment of pellagra but also in the study of some of the fundamental chemical processes involved in its development.

For ease of description, the recent advances in our knowledge of pellagra will be divided arbitrarily into those concerned with: Therapy in the classic case; the vasodilator effect of nicotinic acid and related anti-pellagric compounds; the recognition and therapy of subclinical deficiencies in adults and in children; and the evidences of multiple deficiencies in pellagrins subsisting on their usual deficient diets.

### THErapy IN THE CLASSIC CASE

During the past year and a half, nicotinic acid has been used in treating hundreds of cases of classic pellagra. In this type of case, the outstanding symptoms arise from the skin, the alimentary tract and the nervous system, although all three systems are not necessarily involved nor do the symptoms appear in any regular order.<sup>20</sup>

Characteristic glossitis usually appears early in the course of the disease. In the early stages the tip and lateral margins of the tongue are reddened and swollen. As the involvement of the mucous membranes increases, the swelling and reddening become more intense. Deeply penetrating ulcers are common, and their surfaces are often covered with a thick, gray membrane filled with Vincent's organisms and debris. Stomatitis, gingivitis and pharyngitis likewise may develop and follow a similar course. Burning sensations of the mouth, esophagus and stomach may accompany these oral lesions, and are aggravated by hot or acid foods. Nausea, vomiting, ptyalism and diarrhea, which are frequently present in the severely ill pellagrin, often appear in the sub-clinical case. Anorexia, abdominal distention, pain and discomfort are common symptoms and may be present at any stage of the disease. Dr. Leon Schiff and Dr. Richard Stevens, of the University of Cincinnati School of Medicine, have performed gastroscopic examinations on two pellagrins and noted that the diseased mucous membranes of the stomach are similar in appearance to those of the oral cavity. The mucous membranes of the urethra and vagina are frequently swollen and ulcerated, and appear identical to the affected portions of the alimentary tract.

The dermal lesions of pellagra may develop on any part of the skin although the dorsa of the hands and feet, the axillae, elbows, wrists, knees, areas beneath the breasts, and the perineal region are the most common sites. The lesions are usually bilaterally symmetrical and are separated from the healthy skin by a sharp line of demarcation. At the onset, the affected area is erythematous and often burns and itches severely. Later it becomes swollen, tense, and often fiery red. Sometimes vesicles and bullae develop. After a variable period of time, ranging from a few days to several months, the swelling decreases, the color becomes reddish brown, and desquamation begins. The underlying skin may remain abnormally thickened and permanently pigmented.

Various types of psychoses occur. The most common symptoms are confusion, loss of memory, disorientation and confabulation. One frequently sees excitement, mania, depression and delirium.

The presence of certain symptoms arising from involvement of the peripheral nervous system which, in themselves, are not diagnostic of pellagra frequently helps to confirm the diagnosis. The pellagrin often complains of burning, numbness and tingling of the extremities long before any diagnostic symptoms of the disease appear. (These symptoms are characteristic of peripheral polyneuritis; indeed, pellagrins often have co-existing beriberi.) As the disease in the peripheral nerves increases, alteration of the tendon reflexes occurs; at first their activity is increased, later decreased, and finally absent.

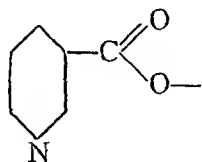
The administration of adequate amounts of nicotinic acid or one of its compounds is followed by the disappearance of many symptoms of the disease. Within 24 to 72 hours, the fiery redness and swelling of the tongue, gums, mouth, throat, and vagina subside, and the associated Vincent's infection disappears. Within 24 to 72 hours, nausea and vomiting cease, increased salivation decreases, and bowel movements become normal. Abdominal distention, pain and discomfort disappear and, in most cases, the desire for food returns. The acute, fiery red erythematous dermal lesions in which the epithelium is intact blanch within 48 hours after the administration of nicotinic acid, but where the continuity of the skin is broken and the lesions are moist, ulcerated, dry or pigmented, there seems to be no specific benefit. Perhaps the most dramatic response of a pellagrin to nicotinic acid therapy is the disappearance of the acute mental symptoms.<sup>18, 15, 17, 18, 21, 22, 23, 24</sup> These symptoms, varying from slight confusion to delirium and mania, disappear rapidly, often over night. The maniacal patients become calm and the confused patients, mentally clear. After therapy they become readjusted, and often have excellent insight and memory of their actions, ideas, and surroundings during the psychotic period. Apathy and lassitude give way to interest. In sharp contrast to the prompt and beneficial response of the mental symptoms to nicotinic acid is the lack of improvement in symptoms arising from the peripheral nervous system. The administration of crystalline vitamin B<sub>1</sub>, however, gives prompt relief from these symptoms.

Nicotinic acid, nicotinic acid amide, and sodium nicotinate are all effective in the treatment of pellagra. They may be administered orally in tablet or capsular form, or parenterally in physiological solution of sodium chloride. Unless the powers of absorption are greatly impaired, oral administration is preferred. Opinion in regard to dosage differs. Although the dosage probably varies considerably in different pellagrins, experience with a large series of cases has shown that 500 milligrams daily, administered orally in 50 milligram doses, is a safe and effective dose for the average case of pellagra. We have observed that only 50 milligrams daily may be required by the mild case but that in rare instances as much as 1000 milligrams per day may be re-

quired for the very severe case. Administered parenterally, the total daily dose varies from 40 to 80 milligrams, dissolved in sterile physiological solution of sodium chloride and injected intravenously, in divided doses of 10 to 15 c.c. each. The dosage of nicotinic acid amide and sodium nicotinate is similar to that of nicotinic acid.

#### VASODILATOR EFFECT OF NICOTINIC ACID AND RELATED ANTI-PELLAGRIC COMPOUNDS

It has been noted by a number of investigators<sup>11, 14, 15, 17, 18, 19, 24, 25</sup> that the administration of large amounts of nicotinic acid to human beings is often followed by sensations of heat and tingling of the skin. This feeling of heat is accompanied by flushing and a rise in skin temperature, especially over the face. Bean and Spies<sup>26</sup> have worked out a method whereby comparable objective determinations may be made. They have found that in normal adults increased temperature of the skin follows the intravenous injection of 20 milligrams of sodium nicotinate, ammonium nicotinate, ethyl nicotinate, and the monoethanolamine salt of nicotinic acid, as well as nicotinic acid itself. This response does not occur following the use of pyridine, quinolinic acid, dinicotinic acid, 2,6-dimethyl dinicotinic acid, beta-amino pyridine, or beta-amino pyridine dihydrochloride. The administration of substances which provoke the vascular response is frequently followed by some epigastric distress, increased peristalsis, and occasionally belching. Observations<sup>26</sup> also show that glycine, under certain circumstances, tends to inhibit this vasodilator reaction. The subcutaneous injection of 1 c.c. adrenalin tends to prevent the elevation of skin temperature following the administration of these drugs. From a study of the structural formulae of these compounds, it is probable that the vascular reaction is associated with the following radical:



Thus, it is evident that the chemicals effective in pellagra therapy do not invariably produce the flushing, although those provoking the temperature rise are all effective therapeutic agents.

#### THE RECOGNITION AND THERAPY OF SUBCLINICAL DEFICIENCIES IN ADULTS AND CHILDREN

The development of severe pellagra can, in most instances, be avoided if the disease is recognized in its early forms and treated appropriately. It is apparent, from a study of many pellagrins, that there is a long prodromal period of ill health. This period has insidiously advancing symptoms, all trivial in nature, but gaining in importance by their persistence. Loss of

weight, strength, and appetite precede the appearance of any diagnostic oral or dermal lesions. During this early stage, ill-defined disturbances of the alimentary tract, including indigestion, "dyspepsia," diarrhea or constipation, as well as weakness and lassitude develop without obvious reason. Irritability, depression, loss of memory, headache and insomnia are noted. Other early symptoms characteristic of a deficiency of the anti-pellagric factors include abdominal pain, burning sensations in various parts of the body, vertigo, numbness, nervousness, palpitation, distractibility, flight of ideas, apprehension, and mental confusion. There is obviously much that is abnormal but nothing which is pathognomonic. The entire syndrome of vague, grumbling complaints appears to be without objective cause and if a patient is seen at this stage of the disease and pellagra is not suspected or suggested, a diagnosis of neurasthenia may be entertained by the physician.

An early diagnosis of pellagra is made possible by the recognition of these prodromal symptoms if they are associated with prolonged subsistence on an inadequate diet; if they occur in persons who have difficulty in ingesting, assimilating, or utilizing food because of organic disease; or if they appear in persons whose requirement for anti-pellagric substances is increased by pregnancy, lactation, hyperthyroidism, infection, or increased physical exercise. The development of clinical pellagra can be prevented in these subclinical cases by the administration of adequate amounts of nicotinic acid. Following its administration these persons experience an increase in sense of well-being and vigor almost immediately. Indigestion is relieved, nausea ceases, and bowel function is restored to normal. Nervousness, irritability, and mental confusion disappear rapidly following adequate dosage, and the vague burning sensations in various parts of the body disappear soon after treatment is initiated. Although improvement in symptoms arising from the alimentary tract and cerebral cortex is striking, many of the pellagrins develop polyneuritis which becomes worse in spite of continued therapy with nicotinic acid or related compounds. (The administration of massive doses of nicotinic acid does not relieve either the painful symptoms of beriberi, arising from involvement of the peripheral nerves, or the symptoms of riboflavin deficiency which arise from the lesions around the mouth, nose, eyes, and ears, whereas the administration of synthetic thiamin hydrochloride and synthetic riboflavin, respectively, is followed by prompt disappearance of these symptoms.)

The amount of nicotinic acid needed to relieve these early symptoms and to prevent the development of clinical pellagra cannot be predicted, nor can it be determined other than by frequent examination of the patient. The amount needed by an individual may vary from time to time and often it is necessary to adjust the dosage to meet this changing need. There is also considerable variation in the amount needed by different patients. As little as 50 milligrams daily may be effective in some cases, while 500 to 1000 milligrams is sometimes required in others, although this is seldom necessary. The therapeutic effect of these substances is proportional not only

to the total dosage, but also to the size and frequency of the individual dose. That is to say, the oral administration of ten doses of 50 milligrams each at hourly intervals is more effective than a single dose of 500 milligrams. This suggests that the controlling factor is the concentration of compounds of nicotinic acid in the blood and tissues.

Observations on the children in several hundred "pellagra families" have shown that many of these children have early clinical signs of pellagra.<sup>15, 24</sup> Such children often have a history as follows: For years they have been somewhat below normal in weight and height; their progress in school has been slow; their inability to concentrate is apparent; and they have few interests. Frequently they complain of poor appetite, indigestion, vomiting, soreness of the tongue and lips, and constipation. Their parents report that they are cross, "fretful," and cry easily. A careful check on the dietary history of the family often shows that the diet of the mother during pregnancy was inadequate and that shortly after birth the child had to be given food of some sort as the mother gave insufficient milk; hence, from a short time after birth, such children have frequently been a "feeding problem." In addition, many of these children show a preference for only one or two foods and refuse all others. The diet is usually rich in carbohydrates, and when milk, eggs and meat are included, they rarely are given in sufficient amounts. When the children have clinical evidence of the disease as shown by characteristic glossitis or dermatitis, there can be no question of the diagnosis, and nicotinic acid therapy is as effective as it is in adult pellagrins. However, spectacular improvement following therapy with nicotinic acid or some closely related anti-pellagic compound has been noted in many children who have subsisted over long periods of time on an inadequate diet but who show none of the diagnostic symptoms of pellagra. In general, the complaints of these children have been similar to those of adults. Likewise, the method of study was similar but the amount of nicotinic acid given was less. Within 24 to 36 hours after the administration of nicotinic acid there was prompt improvement in general health and disappearance of the various complaints. Usually, these children were given a total daily dose, varying from 50 to 300 milligrams. We recommend that this total dose be given in from 5 to 10 tablets at least one hour apart. Children from two to six years of age are usually given tablets of the 10 milligram size, and those up to puberty are given tablets of the 25 milligram size. In treating clinical beriberi and clinical riboflavin deficiency occurring in these children, we gave one-half the amount of synthetic thiamin hydrochloride and synthetic riboflavin recommended below for an adult.

*Abnormal Metabolites.* The appearance of various abnormal metabolites can be detected by laboratory methods before, during, and after the development of the prodromal symptoms of pellagra. Determination of the presence of these metabolites is an important objective test for the recognition of pellagra.

The excretion of abnormal amounts of indican in the urine of pellagrins

is indicative of a disturbance in tryptophane metabolism.<sup>27</sup> Disturbance of porphyrin metabolism is an important part of the pellagra syndrome, as evidenced by the excretion in the urine of pellagrins of increased quantities of porphyrin, and porphyrin-like substances which are ether-soluble red pigments and can be extracted in 25 per cent hydrochloric acid.<sup>28, 29, 30</sup> The content of nicotinic acid derivatives excreted in the urine of pellagrins is greatly decreased during the prodromal period.<sup>31</sup> Similarly, the concentration of cozymase, an enzyme which is fundamental to cellular respiration, is below normal in the blood and urine of severe pellagrins in relapse.<sup>32, 33</sup> The content of vitamin B<sub>1</sub> is often lowered in the urine of pellagrins with beriberi, and the amount of flavin in the urine likewise is decreased in pellagrins with riboflavin deficiency.

#### EVIDENCE FOR MULTIPLE DEFICIENCIES IN PELLAGRINS SUBSISTING ON THEIR USUAL DEFICIENT DIETS

In contrast to the extensive literature on the mental changes of pellagra, relatively few observations have been reported on involvement of the peripheral nerves. While studying so-called "alcoholic" pellagra, Spies and DeWolf<sup>34</sup> came to the conclusion that alcohol is not the sole cause of the peripheral neuritis affecting such pellagrins. The correctness of this point of view has been established by a number of observers. It has also been established that the peripheral neuritis of endemic pellagrins is beriberi and is due to lack of vitamin B<sub>1</sub>.<sup>17, 18, 19, 24, 35</sup>

Still more recent studies on a large series of pellagrins subsisting on their usual inadequate diets, have shown that the administration of nicotinic acid in adequate amounts prevents or improves the alimentary tract symptoms, the erythematous dermal lesions, and the mental symptoms of pellagra, but that it does not prevent, retard or relieve the symptoms of peripheral nerve involvement. These symptoms, however, are relieved when adequate amounts of crystalline vitamin B<sub>1</sub> are administered. Crystalline vitamin B<sub>1</sub> may be administered either orally or parenterally, depending upon the patient's ability to absorb it. For the mild case of pellagra with peripheral neuritis we recommend the oral administration of 10 milligrams twice a day. Severe cases should receive at least twice this amount. The parenteral administration of 50 milligrams daily, in physiologic solution of sodium chloride, by intravenous injection, is preferable in the very severe case as it shortens convalescence and affords prompt relief from pain. The administration of vitamin B<sub>1</sub> should be continued until after improvement has taken place. The acute case will often show improvement within a few hours and the mild case, within 24 to 48 hours. Chronic cases often experience relief from pain within a few days, but some of the abnormal physical signs may remain for a long period of time.

Studies on 25 white and 5 colored ambulatory patients in the nutrition clinic at the Hillman Hospital during 1938-39 show that riboflavin deficiency

occurs in either sex at any age and is not uncommon in persons ingesting, over a considerable period of time, a grossly inadequate diet. It has been pointed out by Sebrell and Butler<sup>30</sup> and by Vilter, Vilter and Spies<sup>32</sup> that this deficiency state is characterized by a feeling of ill health, lack of strength, and loss of weight. Diagnosis depends upon the recognition of characteristic angular stomatitis associated with transverse fissures in the corners of the mouth and lips, and an abnormal shiny redness of the mucous membranes of the lips. Other diagnostic lesions, occurring less frequently, are the comedones giving a "sharkskin" appearance from collections of greasy, seborrheic material around the *alae nasae*, eyes, and occasionally over the ears and malar prominences. Some of these patients give a history of visual disturbances. These symptoms disappear within four to six days following the administration of riboflavin\* in adequate amounts. The minimal and optimal therapeutic dosages have not been determined, but we have found that the oral administration of from 5 to 50 milligrams per day is effective and it seems likely that even smaller doses may be beneficial. Riboflavin is a safe therapeutic agent when administered either orally or intravenously (in sterile physiological solution of sodium chloride). Improvement in these lesions is associated with an increased sense of well being. If these patients continue to eat only their usual diet, the symptoms usually return within 10 to 20 days after the administration of riboflavin is discontinued. (The diet which as a rule consists of corn bread, biscuits, corn syrup, and fat meat, is deficient in riboflavin.) Four patients who were not treated improved temporarily while eating their usual diet at home, but in other untreated cases the lesions slowly and steadily became worse as spring advanced. The daily addition of synthetic riboflavin to the diet of 10 patients has prevented the reappearance of these lesions during the past three months. Two patients have been treated with the phosphoric acid ester of riboflavin,† injected intravenously, with spectacular improvement. Riboflavin deficiency may occur in association with beriberi or pellagra, or it may appear without clinical evidence of either.

The content of coenzyme I and II in the blood and urine is altered little, if any, by the administration of any of the riboflavin preparations tested so far.

The time has come when we are forced to accept the belief that clinical pellagra, clinical beriberi, and clinical flavin deficiency are responses of the body to deprivation of these essential chemical substances over a long period of time. Within our own group we have used the terms "chemical pellagra," "chemical beriberi," and "chemical flavin deficiency" to describe that stage between optimum nutrition and the frank appearance of diagnostic evidence of the particular disease; that is, the period which might be termed the deficiency development time. The latter portion of this period has been

\*Furnished through the courtesy of Dr. Hans Molitor and Dr. Randolph Major of Merck and Company, Rahway, New Jersey.

† Supplied through the courtesy of Dr. O. W. Barlow and Dr. J. B. Rice of the Winthrop Chemical Company, Rensselaer, New York and New York City, New York.



called the prodromal period and is characterized by many vague symptoms of subclinical deficiency states. In such early stages a diagnosis of neurasthenia is apt to be made, yet these symptoms disappear following the administration of specific therapeutic agents.

### DIETARY STUDIES

From an analysis of the dietaries of 50 pellagrins<sup>37</sup> we have learned that in almost every instance, as is shown in the following table, the pellagrin has ingested a diet which is inadequate in calories, protein, calcium, iron, vitamins A, B<sub>1</sub>, G, and, to a lesser extent, vitamin C. The deficiency of calories is manifested in the underweight of the average pellagrin, and the lack of protein, particularly protein of high biological value, is sufficiently pronounced to lead to the edema observed in some cases. The extent of vitamin B<sub>1</sub> and flavin deficiency in the food consumed by these persons is in direct support of our observations that although these dietaries are supplemented with sufficient amounts of nicotinic acid, forestalling the development of alimentary disturbances and mental symptoms of pellagra, the polyneuritis of beriberi frequently develops; and that if adequate supplements of both nicotinic acid and vitamin B<sub>1</sub> are added, preventing the development of pellagra and beriberi, clinical evidence of flavin deficiency develops in some persons. The inadequacy of vitamin A, calcium, phosphorus and iron is

A Comparison of the Nutritive Values of the Dietaries of Pellagrins  
with Standards for Normal People

Nutrient	Calo- ries	Pro- tein	Minerals			Vitamins			
			Ca (gm.)	P (gm.)	Fe (mg.)	A (I.U.)	B (I.U.)	C (I.U.)	G (Sherman- Bourquin units)
Standard* { 19 men	3000	67	.68	1.32	15	5600	150-385	150-375	600-800
27 women	2500	75	.88	1.20	13-15	5600	125-300	125-300	500-800
3 children									
boy—13-15 yrs.	3000	75	.88	1.32	15	5600	150-385	150-375	600-800
boy—4-6 yrs.	1500	55	1.00	1.00	8-11	4200	75-188	100-250	300-650
child under 4 yrs.	1200	45	1.00	1.00	6-9	4200	60-150	100-250	240-600
Per cent patients below standard	97	95	83	85	98	93	95	42	94
Range in per cent below standard	17-91	5-86	7-92	5-92	7-90	1-100	20-100	4-100	17-100
Average per cent below standard	35	50	61	58	51	67	72	47	73

\* From "Quantities of Nutrients for Individuals per Day to Be Used in Evaluating the Adequacy of a Diet"—Dr. Hazel Stiebeling, Bureau of Home Economics, U. S. Dept. Agriculture.

probably accountable, in part, for the general ill health of the patients, although the symptoms of specific mineral or vitamin A deficiency are obscured by the more dramatic symptoms of other deficiencies, or it may be a question of better storage and assimilation of these nutrients. Nicotinic acid, vitamin B<sub>1</sub> and flavin apparently are not stored in the body in available form for a long period of time, since daily supplements given in two or more doses are more effective than the same amount given in one dose or the same amount given at longer than daily intervals.

Preliminary studies concerning the precise physiological effect of synthetic nicotinic acid, riboflavin and its phosphoric acid ester, and cocarboxylase (the pyrophosphate of thiamin) have been undertaken and are summarized below:

Methods, devised independently by Kohn<sup>33</sup> and Vilter, Vilter and Spies,<sup>18, 32</sup> measure the cozymase, a diphosphopyridine nucleotide, and coferment, a triphosphopyridine nucleotide, in blood to approximately one part in 200,000,000.\* Application of this method to pellagrins in relapse shows that their blood and urine contain only a small fraction of the normal concentration of these codehydrogenases. Within 24 to 48 hours after giving large doses of nicotinic acid, there is a striking increase in the concentration of these codehydrogenases in the blood and urine. At the same time that the cozymase and coferment are increasing, improvement occurs clinically. These observations support the hypothesis that nicotinic acid is effective as an anti-pellagic agent, at least in part, through its effect on these codehydrogenases.

Using the extraction method of Emmerie<sup>38</sup> we have noted that the fluorescence of the flavin compound normally excreted in the urine differs somewhat from that produced by equal concentrations of synthetic riboflavin or the phosphoric acid ester of riboflavin, dissolved in water, or in the acid-water-pyridine mixture used in the extraction of urine. Riboflavin and its phosphoric acid ester have a yellowish-green fluorescence, while the flavin compound normally excreted in the urine has a bluish-green fluorescence which is different from the above. When equal molecular quantities of riboflavin or riboflavin phosphoric acid ester are given intravenously, the amount of flavin excreted in the urine during the next few hours is markedly increased and its yellow-green fluorescence is identical with the fluorescence of the synthetic substances. The following day the amount and fluorescence of the flavin extracted from the urine of patients given unphosphorylated riboflavin are essentially the same as they were before therapy. However, the urine of patients given the phosphoric acid ester of riboflavin contains at this time, and for several days thereafter, more extractable flavin than was found during the control period, and this flavin also has the blue-green fluorescence of the flavin compound which is excreted normally. (The quantities are measured with a photoelectrometer and not with a fluorometer because the amount of fluorescence is not directly related to the concentration.) These results might be interpreted as showing that synthetic riboflavin and the synthetic phosphoric acid ester of riboflavin act differently in human beings.

Synthetic cocarboxylase † has been administered intravenously to four

\* We are very grateful to Professor H. von Euler, Biochemiska Institutet, Stockholm, Sweden, for a sample of pure cozymase; and to Herr Geheimrat Doctor Otto Warburg, Kaiser Wilhelm Institut für Zellphysiologie, Berlin-Dahlem, Germany, for pure coferment and pure cozymase.

† Furnished by Dr. Hans Molitor and Dr. Randolph Major of Merck and Company, Rahway, New Jersey.

selected cases of nutritional polyneuritis. The deficient diets of all the patients remained constant throughout the period of study. The administration of synthetic nicotinic acid to two of the patients who had alimentary tract symptoms and skin lesions characteristic of pellagra, was followed by prompt improvement of these pellagrous symptoms but not of the peripheral neuritis. By the end of two weeks the peripheral neuritis had become much worse, and the patients were given sterile physiological solution of sodium chloride for two days without relief from pain. The following day two 10 milligram doses of cocarboxylase were given within two hours, and eight hours after the second dose the patients were relieved of pain. The two patients with clinical beriberi but without co-existing clinical pellagra likewise received no benefit following the injection of sodium chloride, but were relieved promptly after they were given cocarboxylase. These studies show that the intravenous administration of cocarboxylase is effective in relieving pain from nutritional polyneuritis. They do not imply, however, that this material is more effective per unit of weight than is crystalline vitamin B<sub>1</sub>. Cocarboxylase might have some special therapeutic indication, provided the body was unable to phosphorylate vitamin B<sub>1</sub> as a result of liver impairment or some other disease.

Synthetic nicotinic acid, synthetic thiamin hydrochloride, and synthetic riboflavin, as specific therapeutic agents, are invaluable in treating the acutely ill patient for they may be given when it is impossible for the patient to take sufficient vitamin-rich food to make up for these deficiencies. It appears that the improvement in patients with pellagra following the administration of nicotinic acid, in patients with beriberi following the administration of thiamin hydrochloride, and in patients with flavin deficiency following the administration of riboflavin, is brought about by the changing of synthetic substances to enzymes. These, in turn, act through the usual biochemical oxidative-reductive systems in the body. They do not, however, replace all the essential nutrients, and a liberal, well-balanced diet should be given as soon as the patient can take it. These relatively cheap synthetic substances are also valuable as supplements to a diet which, because of economic reasons or poor dietary habits, is inadequate, and in cases where the requirement is increased to such an extent that it cannot be met by food alone.

#### SUMMARY AND CONCLUSIONS

The accumulated information of the past two decades indicates that pellagra is a clinical syndrome caused primarily by a nutritional deficiency, and that certain predisposing and precipitating factors play a rôle in the pathogenesis of the disease. Prominent among these are fatigue, insomnia, loss of teeth, infectious diseases, food fads, chronic alcoholism and diseases affecting the alimentary tract. Failure to recognize the above mentioned conditions in proper light has often led to the designation of such cases as "pseudo pellagra," "secondary pellagra," and "alcoholic pellagra." From

the standpoint of therapy such terms are confusing and should be abandoned, for the disease either is or is not pellagra.

In the absence of the diagnostic triad of cutaneous, alimentary and nervous manifestations, diagnosis of pellagra may be difficult. However, an atypical case may not involve this combination of symptoms but can be recognized when any one of these major systems is affected independently of the other two, and if the possibility of other forms of dermatitis, other diseases of the digestive system, and other diseases of the nervous system is excluded.

An early diagnosis of pellagra is dependent upon a reliable interpretation of an accurate history and a careful physical examination. In the presence of any of the vague symptoms characteristic of the prodromal period subclinical pellagra should be suspected, particularly if there is a history of an inadequate diet. The disease in its subclinical forms is common in both adults and children in poverty-stricken areas where persons live on unbalanced diets low in protein, minerals and vitamins. Early diagnosis and treatment will prevent the development of clinical pellagra.

The appearance of various abnormal metabolites in the urine of pellagrins in relapse and of subclinical pellagrins is an indication of the development of the disease. Detection by laboratory methods of these abnormal metabolites excreted in the urine of pellagrins before, during and after the development of pellagra forms an important objective test for early recognition of the disease and is an aid toward understanding some of the fundamental chemical processes involved.

Preliminary studies directed toward eliciting the precise physiological effect of synthetic nicotinic acid, riboflavin and its phosphoric acid ester, and cocarboxylase have been summarized.

Nicotinic acid or one of its closely related compounds, when administered in adequate amounts, has a prompt and beneficial effect on certain symptoms of clinical and subclinical pellagra. In cases of acute or chronic pellagra in relapse it will: (a) cause fading of the fiery red lesions of the mucous membranes and diminish the Vincent's infection associated with it, (b) in most cases, restore to normal disturbed gastrointestinal function, (c) restore to normal the mental function deranged moderately or severely in acute pellagra, (d) cause fading of the dermal erythema but not cure chronic changes of the skin. In cases of subclinical pellagra, the vague ill-defined symptoms disappear and in persons subject to recurrences of the disease the development of clinical pellagra is prevented. In both clinical and subclinical pellagra, the sense of well-being, one of the attributes of health, is restored. The necessary therapeutic and prophylactic dose varies considerably from patient to patient and from time to time, and is increased by infection, forced physical exercise, and fever. It can be determined only by frequent examination of the patient. The administration of these substances may produce certain typical reactions which, although they may be unpleasant, are transitory and have not been associated with any grave com-

plications nor have they been shown to be harmful in amounts needed for effective anti-pellagric therapy.

Nicotinic acid has no apparent effect upon the peripheral neuritis which is so frequently associated with pellagra. Pellagrins restricted to a pellagra-producing diet and nicotinic acid frequently develop peripheral neuritis, whereas pellagrins with peripheral neuritis who are maintained on a similar diet supplemented with vitamin B<sub>1</sub> but not with nicotinic acid show improvement in their peripheral neuritis, but not in their mucous membrane lesions, alimentary symptoms, erythematous dermal lesions or mental symptoms. However, neither nicotinic acid nor vitamin B<sub>1</sub> will prevent pellagrins from developing evidence of riboflavin deficiency. In view of this it would seem that pellagrins tend to have not only a deficiency of nicotinic acid or substances that act similarly, but also a deficiency of at least two other water-soluble vitamins, vitamin B<sub>1</sub> (thiamin hydrochloride) and riboflavin. The clinical evidences of these deficiencies are a result of the deprivation of these substances over a long period of time. "Chemical pellagra," "chemical beriberi," and "chemical flavin deficiency" are terms suggested to describe the deficiency development time. Whether additional active substances are involved can be determined only by further investigation.

Nicotinic acid, thiamin, and riboflavin are invaluable in treating the pellagrin who has a deficiency of thiamin and flavin. Detailed studies of the food consumed by pellagrins reveal inadequacies of most of the essential nutrients. It is imperative, therefore, to stress this fact that these chemical substances, although invaluable as therapeutic agents, cannot be expected to replace a liberal and well-balanced diet.

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# ATROPHY AND NECROSIS OF THE LIVER WITHOUT JAUNDICE\*

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JAUNDICE is probably the symptom which leads all others in attracting attention to hepatic disease. In its absence, the occurrence of ascites, pruritus, hematemesis, melanoderma, or enlargement of the liver or spleen may indicate the presence of hepatic disease. There are, however, many hepatic conditions not associated with these symptoms and signs and, in such cases, diagnosis must rest largely on suspicion. In the recognition of subclinical cases, a clue is frequently obtained from careful scrutiny of the history and close observation of the patient. In doubtful cases, a review of possible etiologic factors may lead to further search for proof of the presence of a disorder of the liver. The development of various tests for liver function has aided materially in the early recognition or confirmation of the suspicion of hepatic disease.

The cases to be discussed are characterized by the absence of jaundice, are subacute or chronic in nature and illustrate the value of tests for liver function in diagnosis. These cases cannot be correlated definitely with the usual classification of diseases of the liver. Short illustrative reports of cases are presented under the following arbitrary headings: (1) atrophy of the liver associated with disease of the gall-bladder and biliary tract; (2) atrophy associated with syphilis or with its treatment; (3) atrophy of exogenous toxic origin, and (4) atrophy unassociated with other diseases.

## ATROPHY ASSOCIATED WITH DISEASE OF THE GALL-BLADDER AND BILIARY TRACT

*Case 1.* A man, aged 62 years, was first seen at The Mayo Clinic in July 1934. He had had typhoid fever in 1891 and, for 20 years, he had experienced flatulent indigestion. Biliary colic had occurred on two occasions. On physical examination his condition was found to be satisfactory. Cholecystographic examination revealed a poorly functioning gall-bladder containing many stones. Operation was advised but was deferred. The following year he was seen again. Because of vague general symptoms and some decline in health, a bromsulphalein test of liver function was done; results indicated a retention, grade 3 (on the basis of 1 to 4). The van den Bergh reaction was indirect. The concentration of bilirubin was 1.9 mg. per 100 c.c. of serum. Operation again was advised and again was deferred.

This patient related a history of long-standing cholecystic disease and there was evidence of liver dysfunction without jaundice. The latter possibly could be attributable to: (1) a silent stone in the common duct; (2) early cirrhosis secondary to the cholecystic disease; (3) an independent condition, or (4) cholecystitis secondary to a long-standing hepatic disorder. There was nothing in the history to indicate ductal obstruction. It is well

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known that varying degrees of dye retention may be observed with attacks of acute cholecystitis or even after biliary colic. This, however, is usually a transitory phenomenon. In this case, there was no such recent attack and the dye retention would seem indicative of some chronic disorder of the liver. Even with this finding it was impossible to correlate the patient's symptoms either with the cholelithiasis or the hepatic disorder. There was no suggestion in the history of any extraneous toxin and, clinically, we must assume some causal connection between the cholecystic disease and the disease of the liver.

The association of such hepatic disorders with cholecystic disease is of sufficiently frequent occurrence to be suspected more frequently and it should receive due consideration if surgical procedures are anticipated and probably should be a factor in urging such therapy. However, it is well known that surgical procedures for cholecystic disease in the presence of cirrhosis are accompanied by great risk, often accomplish little and, not infrequently, result disastrously. Whether surgery should be undertaken in such cases depends on various factors, including the general condition of the patient, the amount of distress the gallstones are producing and the evidence of significant progression of disease of the liver in which cases tests for liver function give considerable aid.

#### ATROPHY ASSOCIATED WITH SYPHILIS OR WITH ITS TREATMENT

*Case 2.* A woman, aged 40 years, was seen repeatedly at the clinic from 1928 to the present time. On her first visit she complained of a combined deafness of seven years' duration. The liver was slightly enlarged, the edge being two fingers-breadth below the right costal margin. The serology of the blood and spinal fluid was positive for syphilis. A diagnosis of late syphilis of the central nervous system was made. Treatment was instituted and was carried out faithfully. She was seen during the subsequent years for other conditions. In September 1934, the Kline test was 1 +, the Kahn 1 +, the Hinton positive and the Wassermann (Kolmer modification) negative. The Wassermann reaction of the spinal fluid was negative, the Nonne reaction was negative, one lymphocyte was present and the colloidal gold curve was 000,000,211,000,000. Treatment was not given between 1934 and 1936.

In January 1936, she returned because of progressive indigestion of three weeks' duration characterized by impaired appetite, epigastric fullness, distress after meals, belching, nausea, occasional emesis and loss of strength. On examination, there was some tenderness in the epigastrium, the liver extended three to four fingers-breadth below the costal arch and the spleen was palpable. The Kline test was  $\pm$ , the Kahn 2 +, the Hinton positive and the Kolmer negative. The number of erythrocytes and the concentration of hemoglobin were normal. Macrocytosis was not present. Roentgenologic examination of the gall-bladder and stomach gave negative results. The bromsulphalein test indicated retention, graded 4. The van den Bergh reaction was direct. During the subsequent few months, the bromsulphalein retention decreased to grade 3, later to grade 1 and finally to 0. The van den Bergh reaction rapidly became normal. She was placed on a high carbohydrate diet, sodium phosphate was given before breakfast and occasional doses of calomel, mercury with chalk and a little potassium iodide were administered. On February 25, she reported that she was improved. In April, she appeared and felt much better. She progressed to complete recovery.

This patient had syphilis and some enlargement of the liver for a number of years. The syphilis had been treated adequately. The acute digestive symptoms of anorexia, nausea, vomiting and indigestion were very suggestive of hepatic disease and tests of liver function showed definite changes. Under therapy for disease of the liver she recovered. The hepatic disturbance could have been attributable to a recurrence of syphilis in the liver or to a toxic manifestation of the antisyphilitic treatment or to some unknown factor. The syphilologist is inclined too often to consider any development of a new condition in such a case as owing to the syphilis. Although such may be the case, there is reason to believe that some other factor may also be playing an etiologic rôle. The therapeutic test, furthermore, is not conclusive, as other factors, nonspecific in effect, may institute recovery, or the cessation of action of the toxic agent and the natural recuperative powers of the organism may be the chief factors at work. Relapse, as far as serology was concerned, did not occur in this case during this illness and the rate of recovery was more rapid than could be expected in a case of syphilitic hepatitis in view of the amount of mercury administered. The illness probably was not caused by latent toxic effects from previous therapeutic agents, as antisyphilitic drugs had not been given during the preceding two years. Neither was there a history of the use of other toxic agents such as cinchophen or alcohol, nor was there evidence of other systemic disease that would affect the liver. It is our opinion that the illness of this patient was an intercurrent hepatitis of unknown etiology.

#### ATROPHY OF EXOGENOUS TOXIC ORIGIN

*Case 3.* A man, aged 66 years, was examined at the clinic in July 1932. He had suffered from lumbago on three or four occasions in the previous 12 years. In the last four to five years constant lumbar pain with projection of the pain toward the posterior portion of both thighs had been present for which he had taken 170 to 190 tablets of cinchophen with considerable relief.

The edge of the liver was palpable 6 cm. below the costal margin; there was no evidence of ascites or of dilated collateral veins. The movements of the spine were limited. The concentration of bilirubin was 1.8 mg. in each 100 c.c. of serum and the van den Bergh reaction was indirect. The bromsulphalein test of liver function revealed retention of dye, grade 3. The galactose tolerance test gave negative results. The findings on cholecystographic examination were normal. Evidence of hypertrophic changes in the lumbar spine was found on roentgenologic examination. In November 1932, the liver was definitely decreased in size, its surface was smooth and its edge was soft. The degree of retention of dye had diminished to grade 1, the concentration of bilirubin was 1.2 mg. per 100 c.c. of serum and the van den Bergh reaction was indirect. In October 1936, he still complained of pain in both hips, particularly after exercise. Abdominal examination revealed no abnormalities. Dye retention was now absent; the concentration of bilirubin was 1.4 mg. per 100 c.c. of serum and the van den Bergh reaction was indirect.

This patient undoubtedly suffered toxic atrophy or hepatic degeneration without symptoms, apparently owing to the ingestion of cinchophen. The enlargement of the liver and the history of the use of cinchophen led us to

study the liver function. He has made a complete recovery. Numerous similar cases have been encountered, chiefly patients who had gout. The question arises: Should further cinchophen be given to patients who have gout and have such evidence of hepatic injury? Cinchophen has been used with improvement of gout but if gout can be kept under control by dietary methods alone, cinchophen should not be given. However, if the gout is active and severe, cinchophen becomes almost a necessity. Our custom in such cases is to give cinchophen for two or three days each week, in conjunction with sodium bicarbonate and a high carbohydrate diet. Evidence of toxic symptoms or objective evidence, either by clinical or laboratory methods, of disturbance of the liver requires omission of the cinchophen. We have not encountered difficulties by this procedure. Toxic symptoms include anorexia, nausea, epigastric distress, or other gastrointestinal symptoms. Urticaria or other signs of intolerance should not be ignored. If jaundice develops the drug should be discontinued at once.

Cinchophen is only one of many chemicals which may injure the liver. Numerous other drugs have at times a well recognized hepatotoxic effect, such as arsenic, chloroform, carbon tetrachloride, alcohol and phosphorus. In intoxications from these drugs, jaundice may occur in the more severe stages. The practical point is that patients receiving drugs which are known to produce hepatic injury at times, should be observed carefully and proper adjustments should be made if such disturbances develop.

#### ATROPHY UNASSOCIATED WITH OTHER DISEASES

*Case 4.* A man, aged 32 years, son of the patient whose case was reported first in this series, was seen at the clinic in July 1935. Ten years previously he had experienced painless icterus of two weeks' duration, associated with a digestive upset. Since then he has had spells of indigestion lasting from five to seven days and occurring every three or four months, increasing in frequency to the extent of having an attack every one or two weeks. These were characterized by impaired appetite, epigastric distress after eating, sour stomach, belching, constipation, light-colored stools, nausea, headaches, bad taste, sallow color and loss of weight. He felt generally miserable. He had weighed 152 pounds previously but had lost 15 pounds in the three months preceding registration at the clinic. He was an asthenic individual of sallow color. There was slight enlargement of the liver. A cholecystogram revealed a normally functioning gall-bladder. The bromsulphalein test of liver function revealed retention grade 1. The van den Bergh reaction was indirect and the concentration of bilirubin was 1.0 mg. per 100 c.c. of serum. The galactose tolerance test was normal. The Takata-Ara test was strongly positive. The albumin-globulin ratio and the values for serum protein, blood cholesterol and cholesterol esters were normal. Exploration was considered advisable. The appendix was removed. The gall-bladder was normal on inspection and palpation but when removed, it was found to contain a few small papillomata. The stomach, duodenum and pancreas were normal. The consistency of the liver was increased. A fine type of reticular fibrosis could be seen through the capsule. The characteristic irregularity of cirrhosis was not present.

There are several points of interest in this case: (1) the possibility of an inherited tendency to have hepatic disease; (2) the attacks of anorexia,

nausea, indigestion and light-colored stools, which readily could be considered functional in origin, should suggest the possibility of early hepatic disease; (3) in spite of a relatively long history and the appearance of the liver at exploration indicating definite anatomic evidence of injury, hepatic functional tests showed a minimum of abnormal findings and (4) the prognosis in these cases as a rule is not good, the condition often slowly progressing to a definite cirrhosis.

*Case 5.* A woman, aged 50 years, was seen in August 1937. She had had painless jaundice at the age of 12 years, since which time she had suffered from migraine headaches. In the five years preceding admission, the headaches had become progressively less frequent but she suffered attacks of restlessness, insomnia, anorexia, bloating, belching, aching and soreness in the right upper quadrant of the abdomen and light-colored stools. Her color was sallow and there was a history of loss of weight. She had not experienced chills, fever or colic. In December 1936 and in April 1937, she suffered more severe attacks and during the latter one, lost 15 pounds. Physical examination showed no significant abnormalities. The liver and spleen were not enlarged. The concentration of hemoglobin and the number and fragility of the erythrocytes were normal. Macrocytosis was not present. On cholecystographic examination a normally functioning gall-bladder was found. The bromsulphalein test of liver function revealed retention, grade 1. The van den Bergh reaction was direct and the concentration of bilirubin was 1.3 mg. per 100 c.c. of serum. Exploration was advised. This was performed elsewhere and the surgeon reported that, on examination of the liver, gross evidence of cirrhosis was found. The gall-bladder was atrophic and the extrahepatic bile ducts were small. Stones were not found in the gall-bladder or ducts.

This case resembles the preceding case in many respects. The symptoms are similar and the laboratory findings are minimal. The symptoms had many aspects of a functional disturbance, being particularly suggestive of a syndrome of an irritable bowel as encountered among asthenic patients. If disturbance of liver function had not been discovered, such a diagnosis would have been likely. In spite of the long duration of symptoms, only very slight disturbance of liver function was demonstrable by laboratory procedures, and yet at operation there was evidence of gross changes in the liver.

The etiology in these two cases is unknown. This is illustrative of the statement of Osler in regard to many liver conditions: "The absence of an etiologic factor was a remarkable feature of the disease." The significance of the painless jaundice suffered by these patients in earlier years is uncertain. It may indicate an initial injury of the liver and the beginning of a slowly progressive lesion. If such is the case, these patients illustrate well the ideas which Bloomfield<sup>1</sup> recently has expressed.

The last two cases were of a chronic nature and their symptoms were suggestive of disease of the liver. However, physical examination did not reveal enlargement of the liver or spleen. The following two cases are examples of acute mild injury, without symptoms that could be definitely attributed to the liver. The patients enjoyed good health.

*Case 6.* A man, aged 42 years, on routine examination in February 1933, was found to have slight enlargement of the liver. He did not have abdominal complaints. Laboratory tests were normal, including the van den Bergh reaction and concentration of bilirubin. The following year at his routine examination, a bromsulphalein test for liver function revealed retention, grade 2. On cholecystographic examination a normally functioning organ was found. In April 1935, he complained of exhaustion from overwork. The liver and spleen were slightly enlarged. Bromsulphalein retention was grade 1. The concentration of bilirubin was 1.4 mg. per 100 c.c. of serum. The van den Bergh reaction was indirect. The results of other tests were normal. In December 1936, he was enjoying good health and the results of all laboratory tests were normal.

*Case 7.* A man, aged 49 years, was examined in March 1936, at which time he complained of a slight sense of fullness in the right upper portion of the abdomen of about 'seven years' duration, relief from which was obtained by evacuation of the bowel. He had known that his liver was slightly enlarged during this time. Bromsulphalein retention was grade 2. The van den Bergh reaction was direct and the concentration of bilirubin was 1.4 mg. per 100 c.c. of serum. Macrocytosis was not present. The results of the hippuric acid test for liver function were normal as well as the content of serum protein and the albumin-globulin ratio. Roentgenologic examinations of the gall-bladder and stomach revealed no abnormalities. A month later, repetition of the test of liver function showed a dye retention, grade 3. He was seen again in February 1937, at which time he had no subjective symptoms. The edge of the liver extended 1 inch below the right costal margin. Bromsulphalein retention was grade 1. The results of other tests, including those of the van den Bergh reaction, were normal.

The slight enlargement of the liver found on physical examination in these cases stimulated further investigation of its function. Functional studies revealed a retention of bromsulphalein of varying degrees and alteration of the van den Bergh reaction, although other functional tests that were carried out were normal. These patients have been followed from two to four years. Subjectively they have been well, and functional studies now indicate little abnormality. The liver is still slightly enlarged, which, of itself, suggests some abnormality. However, the pathologic process does not at present appear progressive because of the improvement that has occurred. The finding of a functional disturbance at the time of their original observation, in spite of the absence of symptoms, probably indicates the presence of a mild acute or subacute toxic degeneration in a previously and mildly injured organ. The prognosis would appear to be good. A number of patients who had enlargement of the liver and who are without symptoms or demonstrable functional changes have been followed for many years without the occurrence of any symptoms or other signs of progression.

The following three cases represent a group of patients who experienced acute injury of the liver, of unknown etiology, associated with variable symptoms and followed by complete recovery.

*Case 8.* A woman, aged 49 years, was examined in March 1937. For many years she had vomited frequently and many operations had been performed elsewhere because of this symptom, without benefit. There was some evidence of congenital syphilis. Her nervous reactions were very unstable. For the 18 months preceding registration at the clinic, vomiting had been more severe. There had been varying

degrees of pain in the upper part of the abdomen. She had used morphine liberally. On examination she was emaciated and dehydrated. Hypochloremia (plasma chlorides 472 mg. per cent) was present but there was a normal concentration of urea and the carbon dioxide combining power was normal. The concentration of bilirubin was 2.5 mg. per 100 c.c. of serum and the van den Bergh reaction was direct. The bromsulphalein retention was grade 2. On administration of liberal amounts of dextrose and physiologic solution of sodium chloride intravenously, vomiting ceased, she felt and appeared much better, dehydration and hypochloremia were controlled and there was a disappearance of the direct van den Bergh reaction and bromsulphalein retention. Subsequently, she underwent exploration at which time the liver and biliary ducts appeared normal.

The relationship of the functional disturbance of the liver to the hypochloremia, dehydration and symptoms is uncertain. Possibly starvation and dehydration had led to fatty degeneration of the liver which could readily aggravate the nausea and vomiting. Furthermore, the liver plays a definite rôle in the regulation of water, as emphasized by Jones and Eaton.<sup>2</sup> Hypochloremia apparently was owing to the loss of gastric secretion by vomiting and probably had no relation to the disturbances of the liver. Administration of dextrose and physiologic solution of sodium chloride readily corrected both conditions. Gross abnormalities of the liver were not noted at exploration. As the vomiting was considered to be probably of functional origin, the case illustrates the chemical changes caused by functional disorders of long duration as demonstrated by laboratory procedures.

*Case 9.* A woman, aged 63 years, was examined in January 1936, because of nervousness, vague abdominal symptoms, indigestion and constipation. She had been seen on various occasions in the previous 20 years on account of constipation and numerous neurogenic disturbances, but there were no abnormal findings. Examination now revealed slight enlargement and tenderness of the liver. Bromsulphalein retention was grade 3, the concentration of bilirubin was 1.2 mg. per 100 c.c. of serum and the van den Bergh reaction was indirect. Six months later her symptoms were similar. The liver was slightly smaller. Bromsulphalein retention, grade 1, was present. Other laboratory procedures gave normal results. In August 1937, she presented herself again, with similar symptoms. Physical examination and tests for liver function were all normal.

This patient on numerous occasions had presented herself with functional gastrointestinal symptoms. These were possibly somewhat worse at the time liver dysfunction was found. However, because of her neurogenic manifestations, it was uncertain whether there were any additional symptoms that could be attributed to the liver. The slight enlargement of the liver led us to investigate its function. Recovery was complete from the standpoint of laboratory tests. No clues as to the etiology of the hepatic disorder were obvious at any time. The consistency of the liver did not suggest a chronic lesion. Any symptoms attributable to the disorder were obviously mild and, with the rapid recovery and decrease in size of the liver and normal functional tests, the prognosis would appear good.

*Case 10.* A man, aged 34 years, was seen repeatedly between 1932 and 1934, for a duodenal ulcer and sinusitis. In March 1934, a resection of the stomach was

done with excellent results. The liver was grossly normal. In December 1936, he returned because of nervousness, insomnia and periumbilical, abdominal distress of two months' duration. This was associated with anorexia, considerable nausea and a loss of 10 pounds in weight. Physical examination revealed no abnormalities. A faint trace of bile was found in the urine. The number of erythrocytes and the concentration of hemoglobin were normal. Macrocytosis was not present. On cholecystographic examination nothing abnormal was found. Bromsulphalein retention was grade 4, the van den Bergh reaction was direct and the concentration of bilirubin was 1.6 mg. per 100 c.c. of serum. As the result of a high carbohydrate diet and daily injections of dextrose intravenously he showed gradual improvement subjectively and, from a laboratory standpoint, the bromsulphalein retention was grade 3, grade 2 and subsequently, grade 1 during the two weeks after his admission. The van den Bergh reaction remained direct during this time. The elapse of another four weeks was necessary before he recovered. On examination a year later, he was in good health.

This patient's symptoms were acute and rather severe. In the history there was no suggestion of an etiologic factor. The severity of the symptoms and the degree of functional disturbance revealed by the results of various laboratory procedures indicate the presence of a rather severe hepatic injury. Improvement in the laboratory findings coincided with the clinical improvement. The normal condition of the liver at previous exploration and the recovery would indicate the presence of an acute hepatic injury with a favorable prognosis. The case is important in illustrating the necessity for considering such lesions in the explanation of unexplained sudden anorexia and nausea. This case corresponds in many respects to case 2, discussed previously under "Atrophy associated with syphilis or with its treatment" in this paper.

It is well recognized that the liver frequently is affected, without the production of jaundice, during the course of numerous infectious diseases, such as pneumonia, typhoid, malaria, septicemia, rheumatic fever and brucellosis, in which pathologic changes such as cloudy swelling, fatty degeneration or varying degrees of necrosis may occur. The involvement of the liver in cardiac decompensation, gummatous, metastatic and leukemic infiltrations, splenic anemia, exophthalmic goiter, eclampsia, amyloidosis, injuries from arsphenamine and alcohol is frequently unassociated with icterus. Weir and Comfort<sup>3</sup> have reported cases of toxic hepatitis from cinchophen without jaundice. More recently, Snell and Comfort<sup>4</sup> have described cases in which hepatic lesions were associated with extreme atrophy of the pancreas. Jaundice was not present in these cases. Furthermore, an occasional case of fatal acute yellow atrophy of the liver without jaundice has been reported such as that of Wilson and Goodpasture.<sup>5</sup>

The majority of the conditions discussed in the preceding paragraph are more or less well recognized. These conditions either with or without jaundice never have been classified satisfactorily from an etiologic, clinical, or pathologic standpoint and the attempt has not been made to so classify the cases presented in this paper.

In this group of cases the etiology is unknown. Evidence of the

presence of any other known hepatic toxins was not discovered. Jaundice was not present to call attention to the possibility of disease of the liver. In some cases, slight enlargement of the liver was present. In others, indefinite or extremely mild symptoms were present and the laboratory investigation was a more or less empirical procedure in an effort to find some organic explanation of the patients' complaints. The symptoms varied in severity. The sudden appearance of anorexia, nausea, occasional emesis, and epigastric distress, not otherwise explained, should direct attention toward possible disease of the liver. In milder cases, definite active therapy was not indicated. However, subsequent avoidance of substances known to have a toxic effect on the liver should be counselled. In the more severe cases, more active therapy is needed. The standard high carbohydrate diet, supplemented by intravenous dextrose, when necessary, proved adequate in this group of cases.

The pathologic changes are conjectural. Material obtained at necropsy or for biopsy is not available for study. Presumably the changes are degenerative processes, cloudy swelling, fatty degeneration or even some degree of necrosis involving the hepatic cells. The term "atrophy" employed in this paper has been used in a general way to indicate these various diffuse processes. The prognosis is likewise uncertain. Only time will decide this. Patients who have some enlargement of the liver probably have some underlying changes of a more chronic nature and the exacerbation is superimposed at the time of observation. Such exacerbations may occur on varying subsequent occasions and indicate the presence of a more or less progressive process and possibly give rise to other evidence of an extensive and irreparable hepatic disorder. However, in other instances, there is every reason to believe that the episodes encountered were acute, although of varying degrees of severity, that recovery occurred and that the future good health of the patient seemed probable.

#### SUMMARY

Extensive damage of the liver may occur under a variety of circumstances without jaundice or other symptoms or signs suggesting hepatic involvement. In such cases, diagnosis must rest largely on suspicion and the employment of tests of liver function. These disorders may be associated with diseases of the gall-bladder and biliary tract, or with syphilis and antisiphilitic therapy, or may result from the ingestion of exogenous toxins. There are many cases, however, unassociated with other diseases, in which the etiologic factor cannot be discovered. These conditions may be chronic or acute in nature and may or may not give rise to symptoms. In the chronic cases, symptoms include recurring mild indigestion, anorexia, nausea, constipation, headaches, weakness and malaise. The symptoms in the acute conditions are chiefly anorexia, nausea, vomiting, loss of weight and strength, and epigastric discomfort. Physical examination seldom reveals



any findings of significance. Qualitative alteration of the van den Bergh reaction and retention of bromsulphalein are the principal evidences of hepatic disorders from the standpoint of laboratory investigation. A group of cases illustrative of the above facts has been presented.

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# THE ACTION OF PARAHYDROXYPHENYLISOPROPYLAMINE (PAREDRIENE) ON THE HEART; A CLINICAL STUDY OF A NEW EPINEPHRINE-LIKE COMPOUND \*

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It is well established that epinephrine is the most valuable therapeutic agent in the prevention and treatment of cardiac standstill. More recently the more stable compound, ephedrine, has been used in the treatment of the Adams-Stokes syndrome. The action of this drug in increasing ventricular excitability is variable and at times minimal, so that consistent results are not obtained and many therapeutic failures have been reported. In previous studies on the effect of drugs on the cardiac standstill induced by pressure on the carotid sinus,<sup>1</sup> it was found that the standstill could be prevented by a large group of substances related in chemical structure to epinephrine, while substances unrelated in structure were without effect. The intensity of the action increased as the chemical structure of the compound approached that of epinephrine. Ephedrine was the only substance available in these previous studies which was effective when administered by mouth. Ephedrine, however, possesses two features which limit its therapeutic value: (1) the comparative weakness of its action (ratio to epinephrine by this method 1: 2000); (2) unpleasant side actions due to central nervous stimulation when administered in adequate dosage. It was concluded from the previous study<sup>1</sup> that further progress in the therapy of cardiac standstill lay in the direction of the development of stable epinephrine-like compounds having a more intense action than ephedrine.

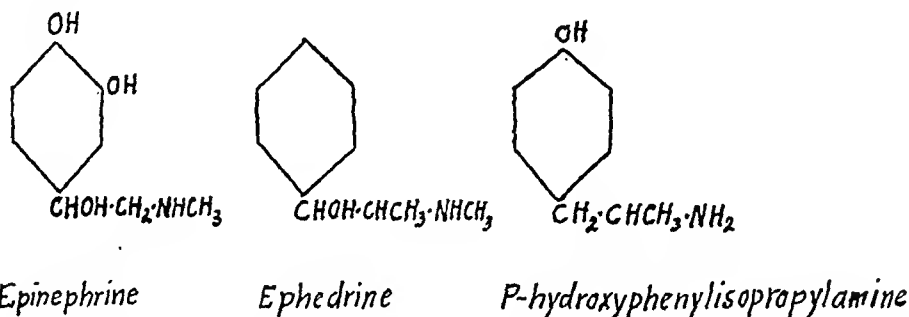


FIG. 1. Chemical structure of epinephrine, ephedrine and parahydroxyphenylisopropylamine (paredrine). (Reprinted by permission from Proc. Soc. Exper. Biol. and Med.)

Paredrine (the name which has been applied to parahydroxyphenylisopropylamine) stands between epinephrine and ephedrine in chemical structure (figure 1). On the basis of chemical structure this substance should

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have a more intense action than ephedrine since it is more closely related to epinephrine. Alles and Prinzmetal<sup>2</sup> have shown that paredrine has a more intense pressor action than phenylisopropylamine. Abbott and Henry<sup>3</sup> concluded that paredrine is about twice as potent as ephedrine in raising blood pressure. In contrast to the hydroxyamines (tyramine, hordenine, the synephrines) previously studied on cardiac standstill by Nathanson,<sup>1</sup> paredrine is effective on oral administration. In the present investigation the action of the drug was studied in three ways: (1) the effect on induced cardiac standstill; (2) the action in heart block; and (3) the modification of the ventricular complex of the electrocardiogram.













### THE EFFECT ON INDUCED CARDIAC STANDSTILL

*Method.* The method utilized has been described in previous publications<sup>1</sup> but will be reviewed here briefly. It depends on the fact that it is possible in many individuals, especially elderly males, to induce a prolonged cardiac standstill by pressure on the right carotid sinus. Pressure on the carotid sinus produces an intense stimulation of the vagus in these subjects and the cardiac standstill is due to a temporary inactivity of the normal cardiac pacemaker—the sinus node, and to a failure of development of secondary centers of impulse initiation. The indication that a drug increases cardiac excitability is demonstrated by the prevention of the cardiac standstill due to the development of an impulse initiating center during carotid sinus stimulation. The rate of the new rhythm is the measure of the intensity of the effect and in this way the comparative actions of various compounds may be studied. Figure 2 shows the comparative activities of a group of epinephrine-like substances studied by this method.

Paredrine-hydrobromide\* was administered by mouth in 14 individuals in whom cardiac standstill could be consistently induced by pressure on the right carotid sinus. In each instance the following procedure was carried out. A control electrocardiogram was made showing the induced cardiac arrest. A single dose of the drug was then administered by mouth which consisted in 12 instances of 60 mg., and in two cases of 40 mg. Electrocardiograms were then taken at intervals and pressure on the carotid sinus repeated. The cardiac standstill was modified in every case. The effect was noticed in 12 cases within 30 minutes after the oral administration of the drug; in two instances the action was not observed until one hour had elapsed. The standstill was abolished in seven individuals by the development of a rhythm, arising in or near the auriculo-ventricular node. In three cases lower ventricular centers became active. In one the rhythm consisted of beats arising from the sinus node alternating with beats arising from an ectopic ventricular focus, while in three instances the sinus node retained its activity. In four subjects the experiment was repeated after an interval of several days or a week, using 100 mg. of ephedrine sulphate. In one

\* The paredrine-hydrobromide was supplied by Smith, Kline and French Laboratories of Philadelphia.

patient 100 mg. of ephedrine sulphate failed to show any effect on the induced cardiac standstill, while 60 mg. of paredrine hydrobromide definitely abolished the standstill (figures 3 and 4). In three instances ephedrine pro-

<u>Comparative Effects on Cardiac Standstill</u> <u>of Compounds Related to Epinephrine</u>		
Drug	Structural Formula	Approximate Ratio of Activity to 1-epinephrine
1-epinephrine		1:1
d-epinephrine		1:20
$\alpha$ -hydroxy $\beta$ -amino 3,4 dihydroxy propyl- benzene		1:10
Synthetic Substance		1:40
Synthetic Substance		1:40
Neosynephrin hydrochloride		1:100
Synephrin tartrate		1:400
Tyramine		1:1,200
Hordenine		1:6,000
Ephedrine		1:1,500 - 1:2,000
Phenylethanolamine		1:8,000
Catechol		Ineffective

The compounds were in the following forms: 1-epinephrine,  $\alpha$ -hydroxy  $\beta$ -amino 3,4 dihydroxy propylbenzene and the first-mentioned "Synthetic Substance" as hydrochlorides; d-epinephrine as the bitartrate; tyramine and hordenine, ephedrine and phenylethanolamine as the sulphates.

FIG. 2. Comparative activities of epinephrine and related compounds on induced cardiac standstill. (Reprinted by permission from Proc. Soc. Exper. Biol. and Med.)

duced qualitatively the same effect as paredrine but the reaction was definitely less intense, in that the effect of the paredrine was observed earlier and the duration was longer (figures 5 to 8). The qualitative similarity of the effect is indicated by the identical contours of the complexes of the beats which were induced by the two drugs. Of special interest was the fact that symptoms which may be attributed to central nervous stimulation were not seen following paredrine. Symptoms such as nervousness, tremor or apprehension were looked for, but were not observed in any case. Headache

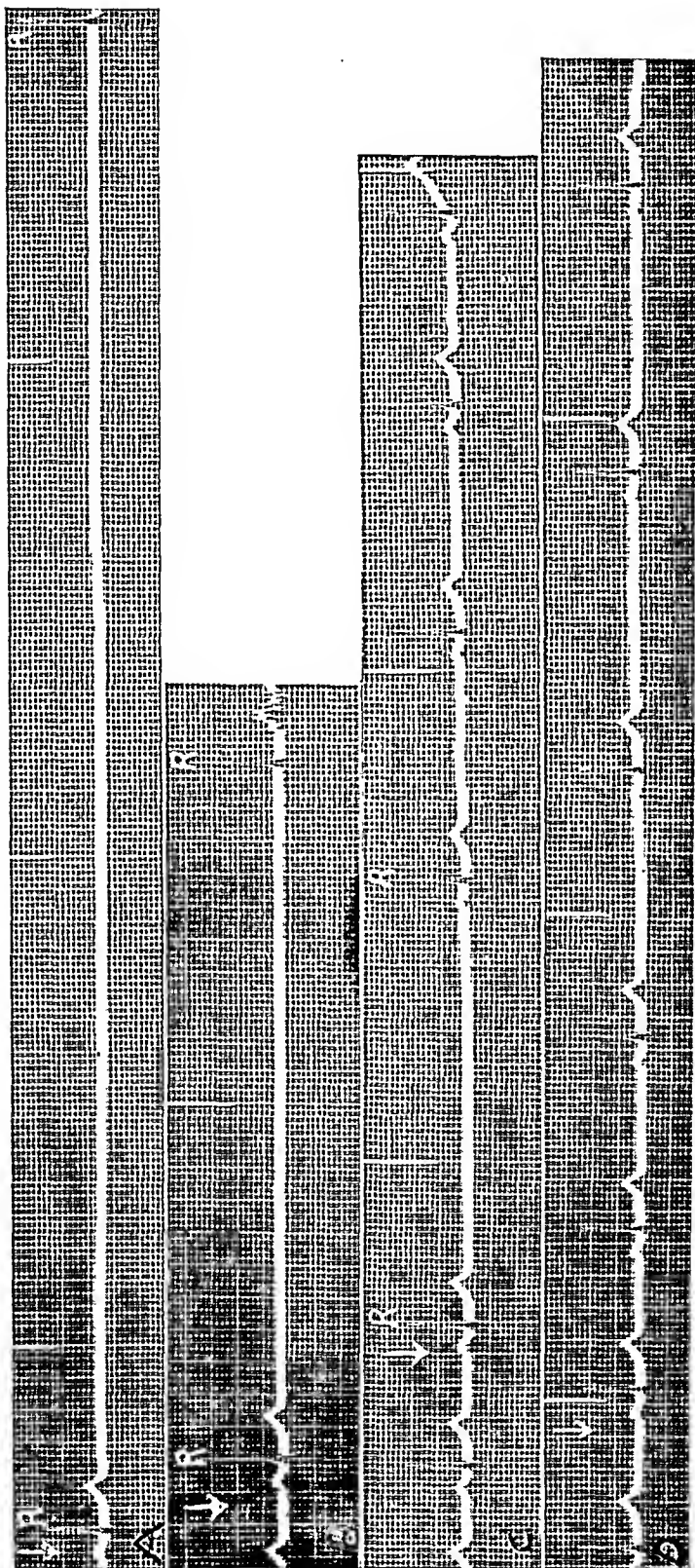


FIG. 3. (Patient B. G.) Strip A shows cardiac standstill of 9 seconds induced by pressure on the right carotid sinus (arrow). Strip B taken 30 minutes after the oral administration of 60 mg. of parendrine hydrobromide, the standstill reduced to 4.4 seconds. C and D taken 60 and 90 minutes after the administration of parendrine. Carotid sinus pressure (arrow) produces only a moderate slowing of the heart.

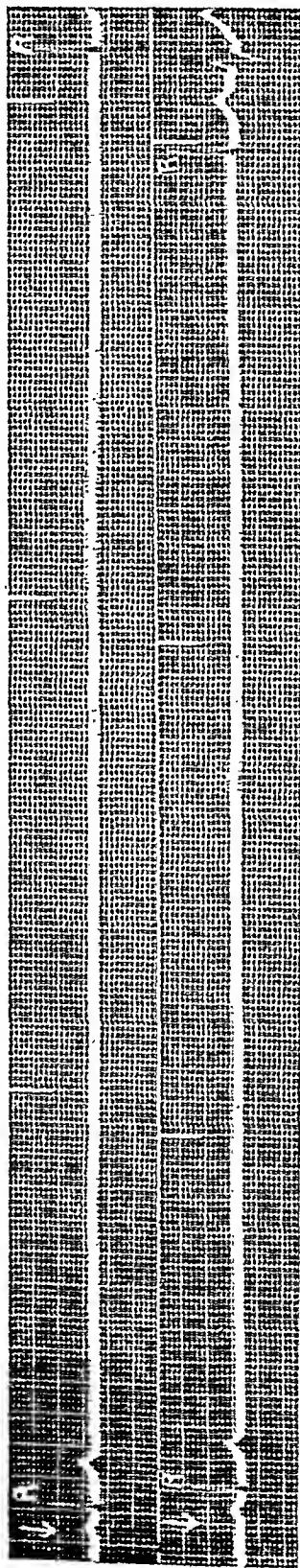


FIG. 4. (Patient B. G.) Upper strip shows cardiac standstill of 8.8 seconds induced by pressure on the right carotid sinus (arrow). After 100 mg. of ephedrine sulphate the cardiac standstill could be reproduced consistently. Lower strip shows the standstill induced 1 hour after the administration of 100 mg. of ephedrine sulphate.

of moderate severity was noted in two patients and this was promptly relieved by the sub-lingual administration of nitroglycerine.

### EFFECT ON HEART BLOCK

Experimental and clinical studies indicate a variable effect of epinephrine in heart block. There is usually a rise in the ventricular rate in complete

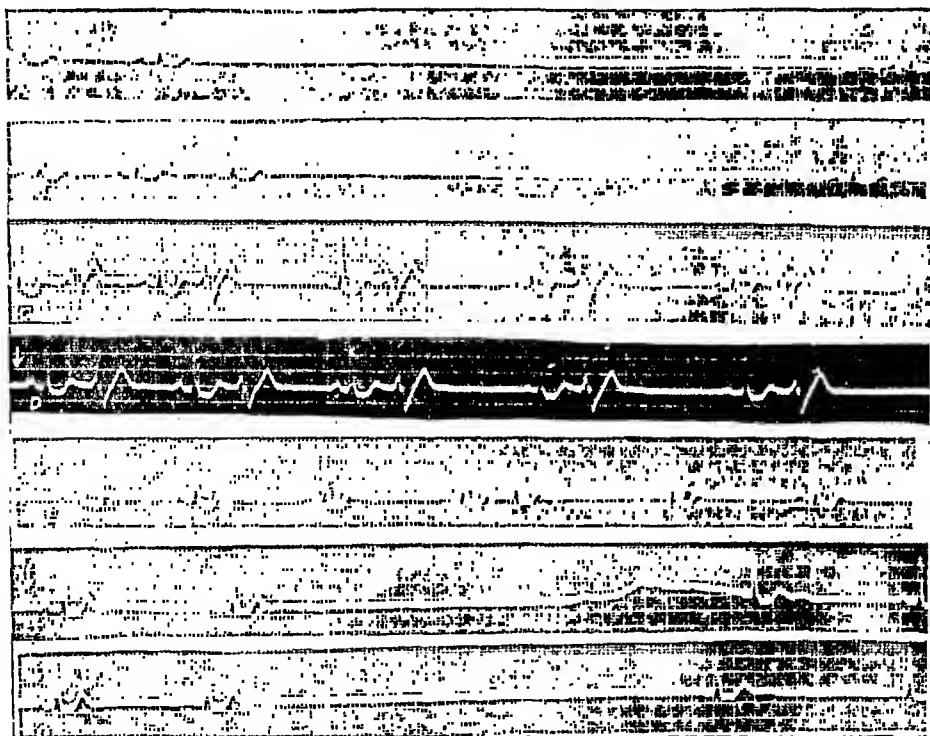


FIG. 5. (Patient G. S.) Strip A shows cardiac standstill of 7.2 seconds induced by pressure on the right carotid sinus (arrow). Lower strips taken at 15-minute intervals following the oral administration of 60 mg. of parahydroxyphenylisopropylamine hydrobromide. Strips C and D show the standstill prevented by the development of beats of auricular and ventricular origin. In strip E the beats are all supraventricular in origin. (Reprinted by permission from Proc. Soc. Exper. Biol. and Med.)

heart block, but this is not constant. The effect on the block is variable. At times there is a lessening or disappearance in the conduction defect but in most instances the block is unaffected. Cullis and Tribe<sup>4</sup> showed that epinephrine increases the ventricular rate both before and after section of the auriculoventricular bundle. Routier<sup>5</sup> produced complete heart block in dogs by crushing the auriculo-ventricular bundle. He then injected  $\frac{1}{20}$  mg. of epinephrine intravenously. The first effect was an acceleration of both chambers, the secondary effect was entire disappearance of the block. Danielopolu and Danulescu<sup>6</sup> in a case of partial block (2:1), reduced the block with epinephrine 1.5 mg. subcutaneously so that only an occasional beat was dropped. Hardoy and Houssay<sup>7</sup> reported a case of complete heart block in which 1 mg. of epinephrine subcutaneously had no effect on the

block or on the heart rate. The same dose intravenously resulted in great acceleration of both auricular and ventricular rates, but no change in the block. Phear and Parkinson<sup>8</sup> reported a case of complete heart block in which epinephrine abolished the syncopal seizures although the block was unaffected and the ventricular rate was not accelerated. Parkinson and

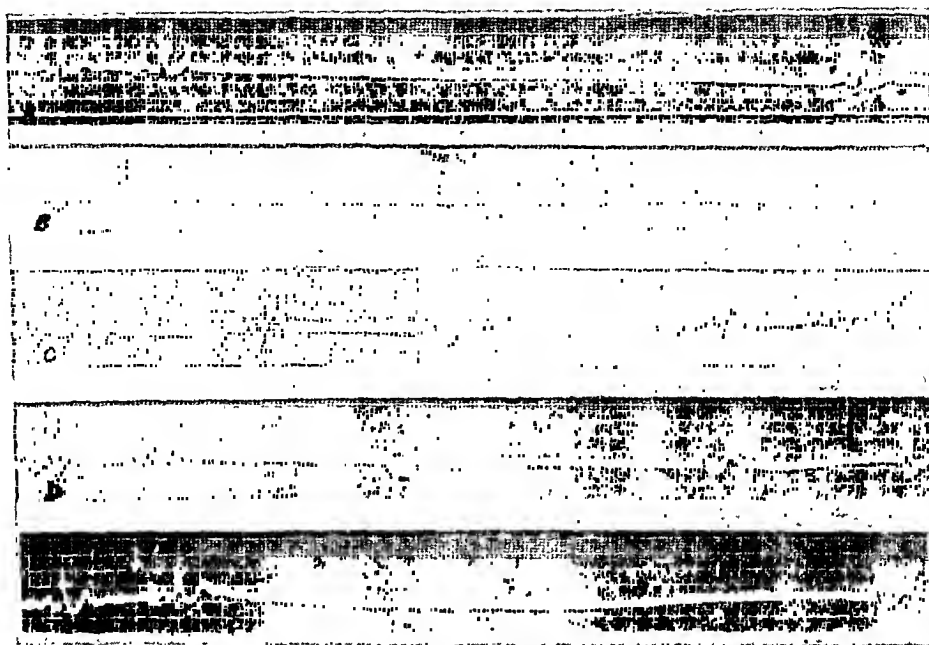


FIG. 6. (Patient G. S.) Strip A shows a cardiac standstill of 7 seconds induced by pressure on the right carotid sinus (arrow). Strip B taken 30 minutes after the oral administration of 100 mg. of ephedrine sulphate. The cardiac standstill can still be induced. Strip C taken 45 minutes after the drug shows the standstill prevented by the development of beats of auricular origin alternating with beats of ventricular origin. D and E taken at 60 and 75 minutes after the drug show the disappearance of the effect. Compare with figure 5 and note that the response to the ephedrine is qualitatively similar but distinctly less intense. (Reprinted by permission from Proc. Soc. Exper. Biol. and Med.)

Bain<sup>9</sup> also reported the disappearance of syncopal seizures but the effect of repeated administration on the same patient was variable. On one occasion there was an increase in the ventricular rate while at another time the rate remained unchanged. When partial block was present in this individual, epinephrine produced an increase in the rate of both auricles and ventricles, and finally restoration of normal rhythm. Feil<sup>10</sup> completely abolished syncopal attacks in a patient suffering from complete heart block by the subcutaneous injection of 0.6 mg. of epinephrine. The block was not influenced and there was only a slight increase in ventricular rate from 29 to 31 a minute. These reports indicate that epinephrine may have the following effects in auriculo-ventricular block: (1) the ventricular rate may be increased and the block remain unaffected; (2) there may be a variable degree of lessening of the block; (3) beneficial effects as indicated by the prevention of syncopal attacks may occur without acceleration of the ventricular rate or the modification of the block. In the present study the effect of the



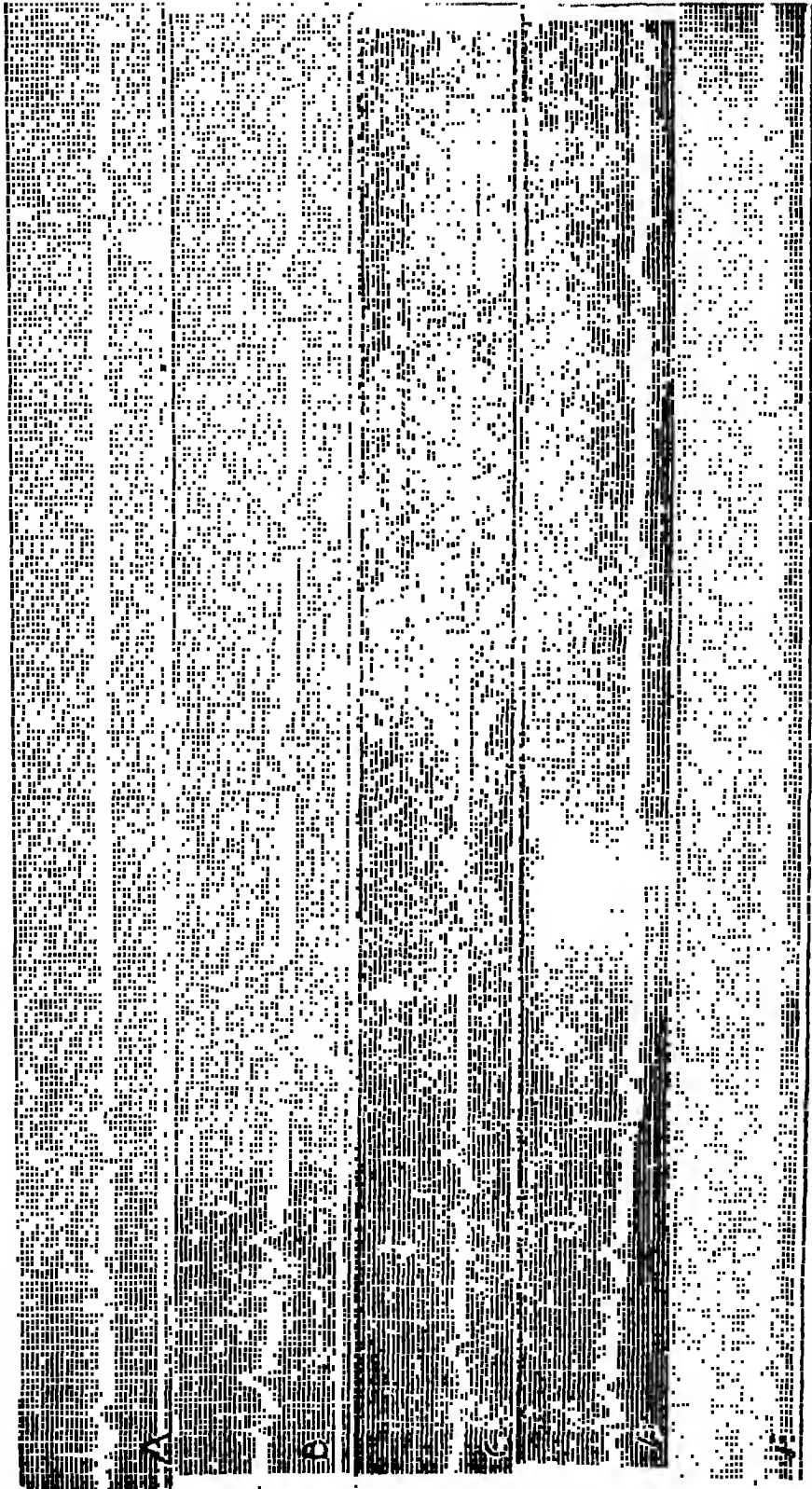


FIG. 7. (Patient J. B.) Strip A shows cardiac standstill of 6 seconds induced by pressure on the right carotid sinus (arrow). Strips B, C, D and E were taken 30, 60, 75 and 90 minutes after the oral administration of 60 mg. of paredrine hydrobromide. Pressure on the carotid sinus is now followed by a nodal rhythm, average rate 38 per minute.

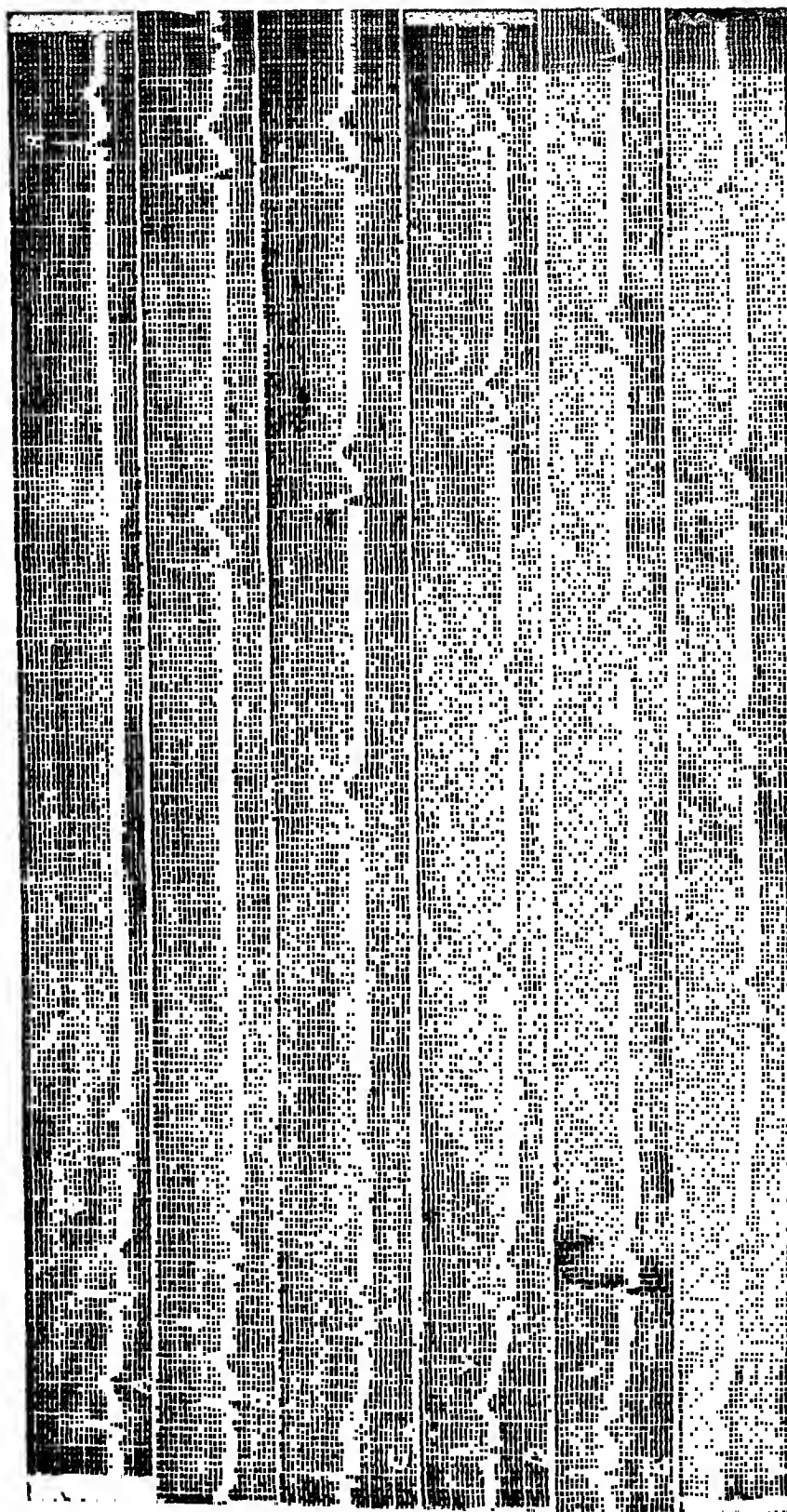


FIG. 8. (Patient J. B.) Strip A shows cardiac standstill of 6.2 seconds induced by pressure on the right carotid sinus. Strip B, taken 30 minutes after the oral administration of 100 mg. of ephedrine sulphate, still shows a standstill of 4 seconds (compare with figure 7 B). Strips C, D, E and F were taken 45, 60, 75 and 90 minutes after the drug and show that pressure on the carotid sinus is followed by a nodal rhythm, average rate 33 per minute.

oral administration of paredrine was observed in six cases of heart block. In four there was complete auriculo-ventricular dissociation and in two instances the block was partial. The following is a summary of these cases:

*Case 1.* Patient T. B. Complete block. Auricular rate 80 per minute, ventricular rate 43.4 per minute. Thirty minutes after 60 mg. of paredrine hydrobromide by mouth the auricular rate was 80, the ventricular rate 44.8. At one hour, and at 90 minutes, the auricular rate was 80 and the ventricular rate was 48.4. At two hours, the ventricular rate was reduced to the original level, 43.4 beats per minute. The block remained complete throughout.

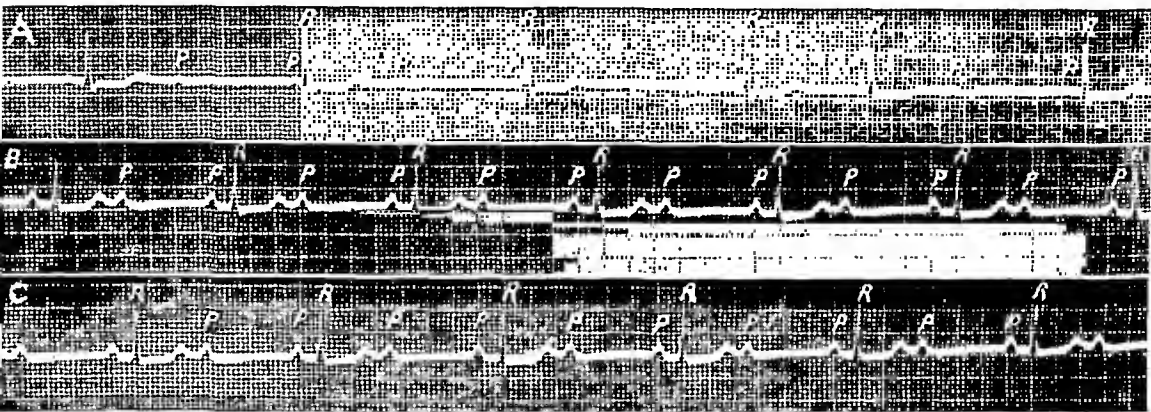


FIG. 9. (Patient M. H.) Strip A shows complete heart block, auricular rate 70 per minute, ventricular rate 34. Strips B and C were taken 60 and 90 minutes after the oral administration of 60 mg. of paredrine hydrobromide. The block is now partial (2 to 1), auricular rate 84, ventricular rate 42. Note increase in amplitude in P-wave in strips B and C.

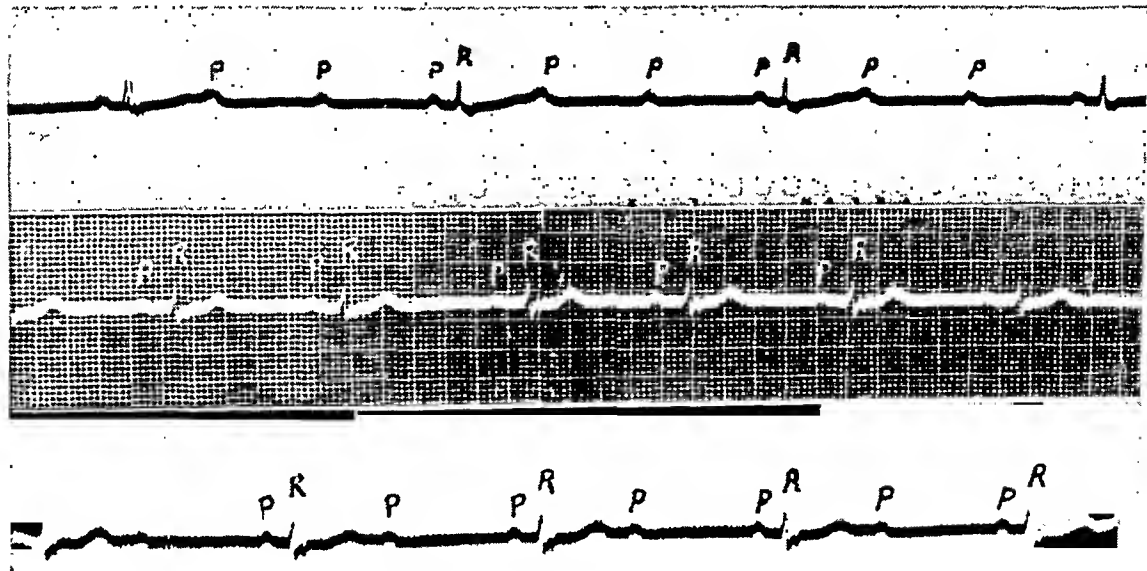


FIG. 10. (Patient J. C.) Strip A shows partial (3 to 1) block, auricular rate 90, ventricular rate 30. Strip B shows the disappearance of the block after the administration of paredrine hydrobromide 60 mg. three times a day for a week. The drug was discontinued for a week and strip C shows return of block (2 to 1) at this time.

Time		Rate	
		Auricular	Ventricular
1:05	Paredrine 60 mg.	78	30
1:35			30
1:50		64	30
2:05		82	46
2:15		90	48
2:25		82	46
2:40		88	46
3:00		84	54

FIG. 11. (Patient M. W.) Complete heart block, showing the effect on the auricular and ventricular rates of 60 mg. of paredrine hydrobromide by mouth.

*Case 2.* Patient M. H. Complete block. Auricular rate 70 per minute, ventricular rate 34 per minute. Sixty minutes after the administration of 60 mg. of paredrine hydrobromide by mouth the mechanism was partial block, 2:1, auricular rate 84, ventricular rate 42. This effect still persisted at 90 minutes when the observations were discontinued. There was a definite increase in the amplitude of the P-wave in the electrocardiogram after the administration of the drug (figure 9).

*Case 3.* Patient J. C. Partial block, 3:1, auricular rate 90, ventricular rate 30. In this patient a dose of 60 mg. was administered three times a day for one week. A record at this time showed the disappearance of the block with a ventricular rate of 58. The drug was then discontinued for a week. The record at this time showed a partial block, 2:1, auricular rate 76, ventricular rate 38 (figure 10).

*Case 4.* Patient M. W. Complete block, auricular rate 78, ventricular rate 30. This patient had been counting his pulse for four years and the rate had never been

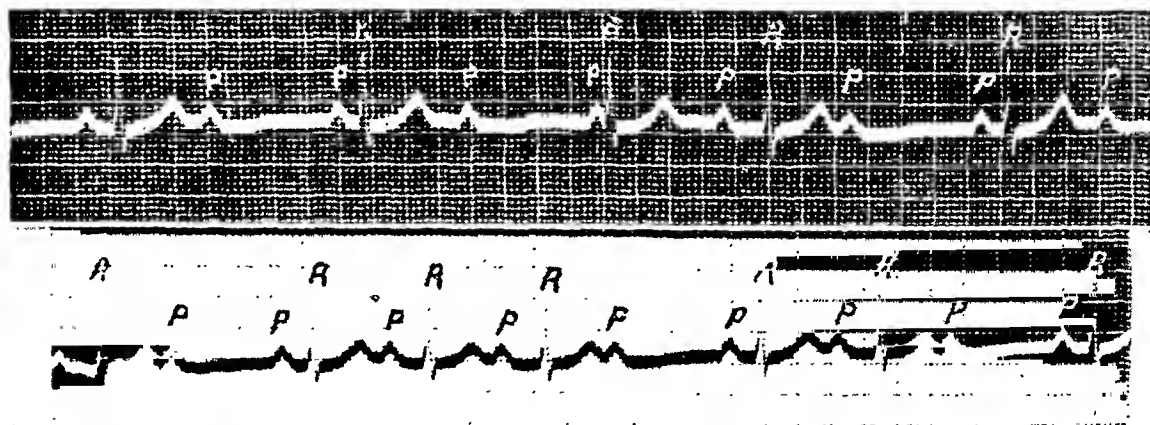


FIG. 12. (Patient J. K.) Upper strip shows complete heart block, auricular rate 82, ventricular rate 48. Lower strip taken 1 hour after the oral administration of 60 mg. of paredrine hydrobromide by mouth shows partial block with dropped beats, auricular rate 94, ventricular rate 66. This effect was reproduced on several occasions.

observed above 30 per minute. After 60 mg. of paredrine hydrobromide by mouth the ventricular rate rose to 46 a minute in 1 hour and to 54 per minute in 2 hours. This effect is shown in figure 11. The increase in ventricular rate was due chiefly to the development of ectopic ventricular beats.

*Case 5.* Patient W. L. Partial block. Auricular rate 64, ventricular rate 32. Paredrine hydrobromide 25 mg. was injected intravenously. In five minutes the

ventricular rate rose to 52 with ventricular beats arising from ectopic foci. At 10 minutes the basic ventricular rate was 36. The mechanism was the same at 30 minutes when the observation was completed.

*Case 6.* Patient J. K. Complete block with frequent syncopal attacks. Auricular rate 82, ventricular rate 48. One hour after 60 mg. of paredrine hydrobromide by mouth there was partial block with the predominant rhythm consisting of two cycles of 1:1 rhythm followed by one cycle of 2:1 block, auricular rate 94, ventricular rate 66 (figure 12). The same mechanism was present 90 minutes after the administration of the drug. Patient received 60 mg. of paredrine three times a day; after a period of two months reported that he had had no further syncopal attacks.

#### EFFECT ON THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM

The effect of epinephrine on the electrocardiogram has been studied in man as well as in animals. Various deviations have been induced by epinephrine but the most consistent alteration is in the T-wave and the R-T interval. Bartos and Burstein<sup>11</sup> noted inversion of the T-wave following

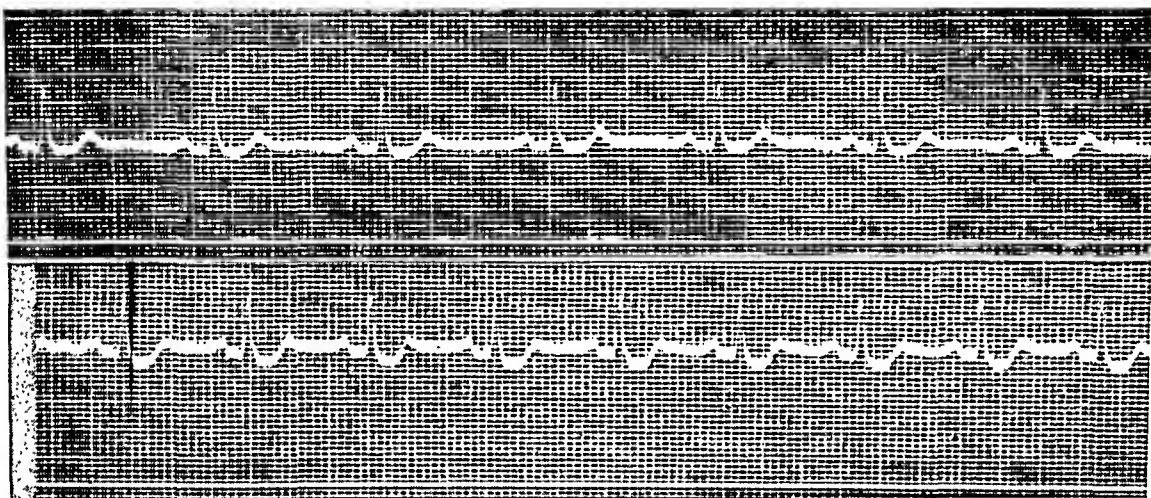


FIG. 13. (Patient G. S.) Upper strip is control record. Lower strip shows definite depression of the R-T segment 1 hour after the oral administration of 60 mg. of paredrine hydrobromide.

injection of 1 to 2 c.c. of a 1:100,000 solution of epinephrine. Katz<sup>12</sup> observed depression of the R-T interval and diminished amplitude of the T-wave following the administration of epinephrine in patients. In a study on the action of epinephrine on the human heart Nathanson<sup>13</sup> observed depression of the S-T and changes in amplitude of the T-wave. More recently, Milles and Smith<sup>14</sup> found that the minimal effect of epinephrine was reduction in the amplitude of the T-wave. Next, directional changes in the T-wave followed: a previously upright T became inverted or vice versa or a marked increase in voltage in the T-wave appeared. Deviation of the S-T interval from the isoelectric line was often associated with the T-wave alterations. Douglas<sup>15</sup> and his associates produced S-T changes resembling those of coronary occlusion by the administration of epinephrine to cats.

In the present study, modifications of the electrocardiogram were frequently observed after the oral administration of paredrine. Of 12 individuals in whom a dose of 60 mg. was administered, the R-T segment was depressed in four and slightly elevated in one instance. The T-wave was increased in amplitude in seven, and depressed in five. In two cases, the chest lead was studied following the administration of paredrine. In one instance the normally inverted T of the chest lead became more deeply inverted. In the other case the patient developed cardiac pain after the administration of 60 mg. of paredrine. The ventricular complex became monophasic, with marked elevation of the R-T segment, resembling the

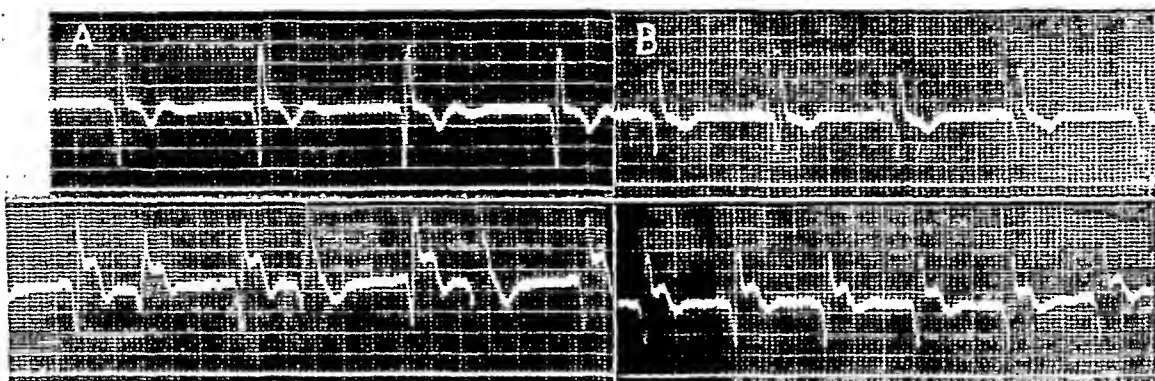


FIG. 14. (Patient G. S.) A, upper strip, control record of precordial lead (chest electrode over apex, indifferent electrode on left leg). Lower strip shows monophasic curve with marked elevation of R-T segment 1 hour after the oral administration of 60 mg. of paredrine hydrobromide. B, upper strip, control record of precordial lead. Lower strip shows the precordial electrocardiogram taken 1 hour after the oral administration of 100 mg. of ephedrine sulphate.

changes which follow acute coronary obstruction (figure 13). In a subsequent experiment 100 mg. of ephedrine sulphate by mouth produced a similar change in the electrocardiogram of this patient. The similarity in the modifications of the electrocardiogram following the administration of epinephrine and paredrine is further evidence of the epinephrine-like action of paredrine on the heart.

#### COMMENT

The results of this study indicate that paredrine exerts an epinephrine-like action on the heart. This is shown by the effect on induced cardiac standstill, by its action on heart block and by the modification of the ventricular complex of the electrocardiogram. The effect of paredrine is less intense but more prolonged than that of epinephrine. The chief advantage of paredrine lies in its stability so that the drug is effective on oral administration. The superiority over ephedrine is its greater intensity of action and the absence of unpleasant side effects. The therapeutic indication for paredrine in cardiac disease is therefore the same as for epinephrine and ephedrine, which is primarily the prevention and treatment of cardiac



standstill. In heart block associated with syncopal attacks a drug effective by mouth is frequently desirable. The present studies indicate that paredrine is the most active epinephrine-like compound for the purpose. A dose of 40 to 60 mg. three or four times a day appears to be sufficient to raise ventricular rhythmicity to a degree so that the tendency to ventricular standstill is definitely lessened. Another indication is the prevention of the asystole associated with the hypersensitive carotid sinus, a syndrome which has been described by Weiss and Baker.<sup>16</sup> Three of the 14 individuals of the present study in whom cardiac standstill could be induced suffered from spontaneous attacks of syncope and were relieved by the administration of the drug.

### SUMMARY

1. Parahydroxyphenylisopropylamine (paredrine) is a drug related in chemical structure to epinephrine and ephedrine.
2. The substance is effective on oral administration.
3. Paredrine effectively prevents the cardiac standstill induced by pressure on the carotid sinus and is at least twice as effective as ephedrine in this action.
4. When administered in dosage effective in preventing cardiac standstill, paredrine does not produce unpleasant side effects due to central nervous stimulation.
5. Paredrine has an epinephrine-like action in auriculo-ventricular block.
6. Paredrine produces changes in the ventricular complex of the electrocardiogram similar to those which follow the administration of epinephrine.
7. Paredrine has certain advantages over epinephrine and ephedrine in the therapy of cardiac and ventricular standstill.

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# TOLERANCE AND TOXICITY OF INSULIN

## III. PROTAMINE AND ZINC COMPOUNDS\*

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COMPLETION of the desired range of experiments was prevented by circumstances. The material used was the regular preparation of protamine zinc insulin as supplied by Eli Lilly & Co. for clinical use. The results, though fragmentary, establish several new facts, as follows.

### I. PROTAMINE INSULIN WITH SPONTANEOUS EATING

These observations were limited to rats. As mentioned in the previous paper, it has never been possible to produce extreme obesity in adult animals of any species with regular insulin. MacKay and Callaway<sup>1</sup> have recently reported the interesting discovery that this can be accomplished in rats with doses of about eight units of protamine insulin, given once or twice daily. The great and sustained increase of appetite is the remarkable feature in comparison with regular insulin.

The present work dealt only with brief experiments, usually with larger doses, and therefore this fattening effect was missed. Another difference as regards appetite was encountered, however, in the form of a failure of appetite with higher doses. Whereas average sized rats will continue to eat moist bread in sufficient quantities to keep themselves safe with doses of 300 to 1000 units of regular insulin, the tolerance for protamine insulin is far lower. With single doses of 10 to 20 units or more, if the rats are unwatched occasional ones are found dead, and this mortality increases as the doses are either increased or repeated from day to day. Although there have been no sufficiently thorough tests to establish a precise limit, it has not been feasible to give single injections as high as 50 or 60 units with spontaneous eating, because of loss of appetite. With lower doses the rats under continuous watch can be injected with glucose at the first sign of hypoglycemia; they will then sometimes resume eating and can be saved by a combination of feeding and occasional glucose injections. With doses of 50 units or sometimes less this combination seems to fail, and recourse must be had entirely to parenteral injections, the difficulties of which are described below.

### II. PROTAMINE INSULIN AND PARENTERAL GLUCOSE INJECTIONS IN RATS

It was shown in the previous paper that fasting rats can tolerate above 100 units of regular insulin with the aid of subcutaneous glucose injections.

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From St. Michael's Hospital, Newark, New Jersey.

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It is therefore a surprise to find that an injection of 10 to 15 units of protamine insulin is fatal for an ordinary sized fasting rat; deaths may occur after as little as five units, and only exceptionally large rats (350 to 450 gm.) can survive as much as 20 units. A direct toxic effect of the insulinate here is excluded. The determining factor is the relentless persistence of the

TABLE I  
Rats—Protamine Insulin with Parenteral Glucose Administration

No. of Animals	Weight gm.	Protamine insulin units	Hours before 1st re-action	Glucose in 1st 12 hrs. gm.	Glucose in 2nd 12 hrs. gm.	Glucose for re-maining period gm.	Total glucose gm.	Total hours of treatment	Result
		Subcutaneously							
3	120-180	5	2½-4	1.5-2.5	2.7-3	0 -9.8	5.2-14.3	24-53	2 lived, 1 died.
8	90-200	10	4½-8	1.4-2.8	2.0-3.3	5.2-7.4	6.8-13.1	50-58	Progressive weakness, dyspnea, hydremia. Death.
5	140-250	15	3½-5	2.2-4.2	3.0-3.8	4.6-6.8	9.9-14.4	28-42	Same.
6	95-190	20	1½-4½	1.8-3.0	1.8-3.0	4.1-7.2	7.9-13.0	24-37	Same.
3	350-440	20	2 -3	2 -2.5	1.5-2	1.2-1.5	4.8- 5.8	32-40	Weakness, subnormal temperature. Recovery.
3	120-190	30-40	2½-3½	1.5-2.7	2.8-3.8	3.0-7.6	7.1-13.8	38-57	Weakness, etc. Death.
3	110-195	50-60	3 -4½	1.0-2.1	3.2-4.0	3.9-11.0	7.9-16.8	36-44	Same.
2	120-160	100	2 -3½	1.6-3.1	2.8-4.2	3.3-6.8	8.2-14.0	34-48	Same.
2	125-200	150	1½-2½	2.5-3.0	4.5-5.8	6.2-10.8	12.8-19.0	32-45	Same.
		Intravenously							
1	100	40	2½	1.5	0.5	—	2.0	15	Sudden death.
1	110	150	3½	3.0	1.6	0.3	4.9	25	Progressive weakness. Death.
1	135	300	2	2.5	2.1	2.5	7.1	40	Weakness progressing to death 15 hours after last injection. Autopsy blood sugar 160.

insulin activity, which continues until the glucose injections reach an amount which is fatal to any rat. Depending upon the individual strength and other variables, it is seen in the table that a dose of as little as 10 units may keep up its effect for as long as 58 hours. Many blood counts (not tabulated) have shown marked hydremia.

Though the duration is so much longer, the intensity of the action is not greatly different from that of ordinary insulin, as judged either by the interval before the first hypoglycemic attack, or after that by the hourly demand for injected glucose. There are some clinical reports which indicate that protamine insulin has a higher glucose equivalent than ordinary insulin. Since the conditions are exaggerated in animals, because of the much longer activity, there is a plainer demonstration that the essential difference is merely one of time. The fallacy of insulin-glucose ratios is thus further illustrated, because comparisons of both the total glucose equivalency of regular and protamine insulin and the hour-by-hour effect of small versus large protamine insulin doses are reduced to absurdity in these animal experiments.

The results of intravenous injections in only three animals must be viewed as suggestive rather than conclusive. The impression is conveyed that protamine insulin is more toxic than regular insulin, because a dose as

low as 40 units was fatal. This effect, however, can scarcely demonstrate a direct toxicity of the insulinate itself, since, by a peculiar accident, the survival with 300 units was longer than with smaller doses.

With reference to glucose metabolism, there seems to be the usual indication of inferior potency of insulin by the intravenous as compared with the subcutaneous route. Though all three animals died, they lived long enough to prove decisively (cf. previous paper) that protamine insulin has a more prolonged effect than regular insulin also with intravenous administration. This statement applies to large doses, which presumably cause a passage of some unchanged protamine insulin into the tissues, from which it may be absorbed gradually. The identical effects of regular and protamine insulin intravenously were obtained by Longwell and Ravin<sup>2</sup> with doses of only 1.5 units per kg. in rabbits. Similar differences prevail with subcutaneous dosage; the effects of large doses in human patients may last into the third day (Lawrence and Archer<sup>3</sup>; Sprague and Rynearson<sup>4</sup>), while the smallest doses show no difference from regular insulin (Patel and Rönmark<sup>5</sup>; Wilder and Wilbur<sup>6</sup>).

### III. ANTIDOTING BY COMBINED FEEDING AND GLUCOSE INJECTIONS

Some of the preceding remarks are further illustrated by table 2. It may be noticed that the rats could be saved after doses up to 40 units, but after 60 units or more all died.

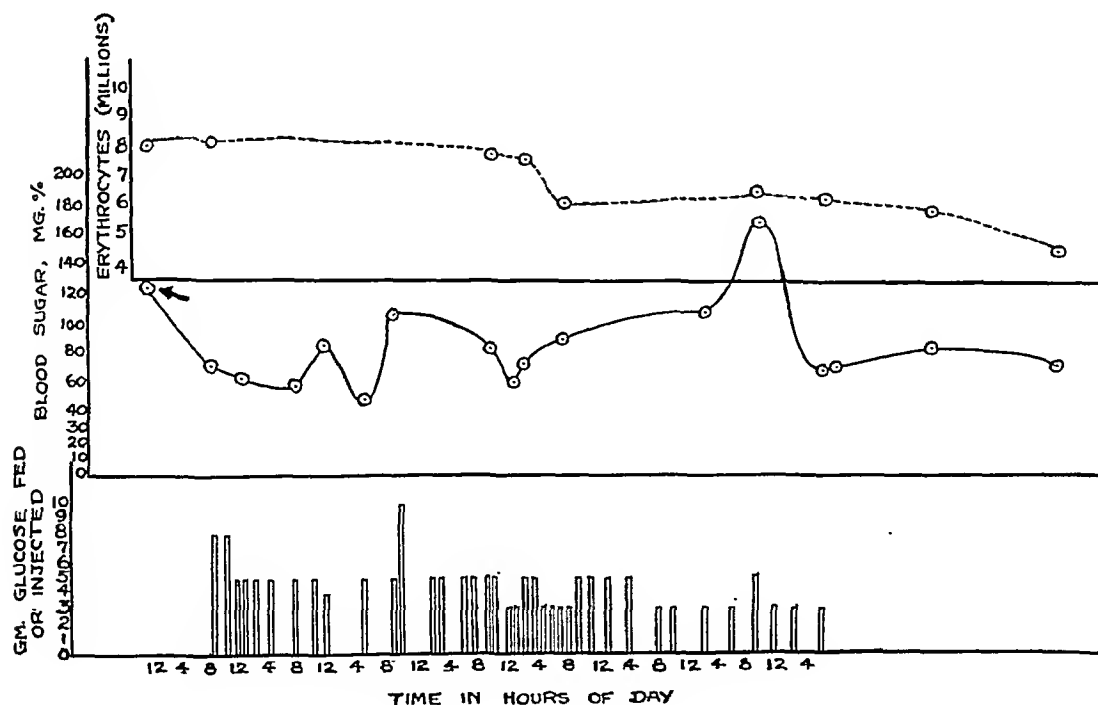


FIG. 1. Rat 401N; weight 215 gm. 15 units protamine insulin subcutaneously. Arrow shows time of injection.

The method of saving life consists in sparing the animals from the injury of too long continued parenteral glucose injections. Thus, by feeding

either bread or glucose for one or two days after the insulin injection, the survival period can be lengthened, and a separate record (figure 1) shows how a strong rat was saved in this way after 15 units of protamine insulin, which continued to cause hypoglycemic convulsions for 90 hours. Also, if appetite is retained, feeding may replace injections on some of the later days and the rat may thus survive. Rats 3, 4 and 5 in table 2 show how life may

TABLE II  
Rats—Subcutaneous Injections of Regular or Protamine Insulin;  
Carbohydrate Feeding; Glucose Injections

Rat No.	Weight gm.	Insulin dosage. Units	CH in 1st 24 hrs.		CH in 2nd 24 hrs.		CH in 3rd 24 hrs.		Total hrs. of treatment	Result
			Fed gm.	Glucose injected gm.	Fed gm.	Glucose injected gm.	Fed gm.	Glucose injected gm.		
1	215	15 P	5 bread	0	0	1.5	0	4.3	120	Glucose injections, 4.8 gm. in 4th 24 hrs., 2.0 in 5th 24 hrs. Progressive weakness. Death with normal blood sugar.
2	250	15 P	4 bread	0	3.2 glucose	0	2.0 glucose	1.8	124	Glucose injections, 3.6 gm. in 4th 24 hrs., 2.4 gm. in 5th 24 hrs., 1.0 gm. in last 4 hrs. Lived.
3	130	20 P	9 bread	0	5 bread	1.0	1.4 glucose	1.0	72	Moderate weakness. Fed ad libitum after 72 hrs. Lived.
4	150	20 P	8 bread	0	3.6 glucose	0	3 glucose	0	72	Fed ad libitum after 72 hrs. Lived.
5	150	40 P	12 bread	0	3 bread	3	—	—	48	Fed ad libitum after 48 hrs. Lived.
6	140	40 P	6 bread 2 glucose	0	4 bread	2	—	—	48	Food omitted after 48 hrs. Hypoglycemic death.
7	185	60 P	12 bread	0	6 bread	0.5	6 bread	0	72	Died in sudden unexpected hypoglycemic attack.
8	150	80 P	10 bread	0	7 bread	0	5 bread	1.2	72	Died in sudden convulsion, probably hypoglycemic.
9	100	2×40 P, 15 hr. intervals	0	5.6	0	4.2	0	1.0	54	Progressive weakness. Death.
10	135	3×10 P, 15 hr. intervals	11 bread	0	0	5.0	0	4.8	90	Glucose injections 4.0 gm. in last 18 hrs. Weakness. Death.
11	290 obese	3×20 P, 18 hr. intervals	0	0.9	0	4.5	0	4.1	114	No glucose required for first 12 hrs. Total injected 16.8 gm. Progressive weakness. Death.
12	140	3×150 regular insulin, 12 hr. intervals	15 bread	0	5 bread 2 glucose	2.0	—	—	36	Apparent recovery; sudden death at 48th hr.
13	170	8×100 regular insulin, 12 hr. intervals	16 bread	0	2.5 glucose	0	3.0	0	120	Glucose 2.4 gm. eaten in 4th 24 hr., 2.7 gm. injected in 5th 24 hr. Lived.

thus be saved after 48 or 72 hours, after doses as high as 20 or 40 units. But (rat 6) if both feeding and glucose injections are withheld after 48 hours, hypoglycemic death results.

With the largest doses this device fails to save life, because of the failure of appetite or strength, due apparently to a direct toxic action of the insulin independent of excess or deficiency of glucose. As above mentioned,

this effect is produced by much smaller doses of protamine insulin than of regular insulin.

Rats 9, 10 and 11 show how doses of 10 to 40 units of protamine insulin (which singly permit of survival, because appetite is retained) may become fatal when repeated two or three times at intervals of 15 to 18 hours. The rats could not be saved by feeding on the later days because they had lost appetite; therefore they succumbed to the continued glucose injections.

A comparison of insulin-glucose ratios (at least as obtained with the method in clinical use, namely subcutaneous insulin injections) may be made between rats 1 and 2, which received single injections of protamine insulin, and rat 13, which received 800 units of regular insulin divided into eight injections of 100 units each 12 hours apart. The duration of the hypoglycemic effect was practically identical in the three animals, namely 120 to 124 hours. Furthermore the total amount of carbohydrate required for antidoting the 800 units was not very greatly different from that required for the 15 units.

One of these three rats (number 11) furnished an example of exceptional individual tolerance (perhaps due to obesity) in that it could remain symptom-free for 12 hours after 20 units of protamine insulin, and required only 0.9 gm. of glucose for the rest of the 24 hours.

In respect to carbohydrate metabolism, the 800 units of regular insulin was very slightly superior to the 15 units of protamine insulin in intensity of effect, as judged by the consumption of glucose in the hourly periods. Furthermore this effect was continuous, since the active period of 15 to 24 hours for a single dose of 100 units of regular insulin (as shown in the previous paper) must entail a large overlapping of these 12-hourly injections. Nevertheless rat 13 retained appetite for almost the entire time, and the intoxication and death which follow sufficiently large single doses of either regular or protamine insulin remained absent. Furthermore the hypoglycemic tendency ceased within 24 hours after the last insulin injection; in other words there was little or no cumulative effect as compared with a single dose of 100 units, and nothing like the duration of 48 hours or more which is demonstrable for single doses of 250 or 300 units of regular insulin.

#### IV. PROTAMINE INSULIN WITH PARENTERAL GLUCOSE ADMINISTRATION IN CATS AND RABBITS

The uniform fatalities after doses of 150 or 200 units in table 3 seem explainable at least in some instances entirely by the amount of injected glucose. A direct toxic action of the insulinate is evident in some instances; nevertheless with 1000 units the survival was not shortened beyond the limits of accidental variation. The deaths occurred without hypoglycemia, and too early to afford any information as to the possible duration of effects of the subcutaneous injections. The interval before the first convulsive reaction was not greatly different from after regular insulin. The usual hy-dremia, attributed to the glucose injections, was present.

The three intravenous experiments were chaotic. Without preliminary fasting, and with the same dose of 200 units one rabbit died of unknown cause within three hours. The second showed merely nervous symptoms, without acute attacks, for 20 hours. Then a repetition of the dose gave a typical effect in the form of a shortened interval before reaction ( $1\frac{3}{4}$  hours), weakness, hydremia and death. Since it is certain that 200 units of regular insulin under the same conditions will not cause hypoglycemia lasting 34 hours, this experiment confirms the greater duration of the effects of protamine insulin as compared with regular insulin intravenously.

TABLE III  
Cats and Rabbits—Protamine Insulin with Parenteral Glucose Administration

Animals	Weight kg.	Protamine insulin units	Hrs. before 1st reaction	Total glucose required gm.	Total hrs. of treatment	Initial erythrocyte count. Millions	Final erythrocyte count. Millions	Final blood sugar mg.	Result
Cat 1	3.7	Subcutaneously 200	5½	58	30	—	—	150	Prolonged prostration. Death. Prostration. Rectal temperature 32° C. Blood concentration due to 20% glucose solution.
Cat 2	3.0	1000	—	42	26	7.8	12.5	187	
Rabbit 1	2.2	10	4½	2	7	—	—	—	Easy recovery.
" 2	3.0	20	4	1	4	—	—	—	Easy recovery.
" 3	2.6	50	10	4	14	—	—	240	Death in convulsions, with hyperglycemia.
" 4	3.0	50	5½	26	24½	—	—	68	Death in convulsions.
" 5	2.0	150	3	37	36	—	—	290	Progressive weakness. Convulsions with hyperglycemia. Death.
" 6	3.1	180	3½	10	17	—	—	156	Easy recovery.
" 7	2.0	200	2½	17	22	—	—	65	Progressive weakness. Death.
" 8	1.8	200	2¼	23	21	7.8	3.4	110	Progressive weakness. Death.
" 9	2.2	200	3	26	31	8.4	3.0	290	Progressive weakness. Death.
" 10	2.0	Intravenously 200	—	20	5	7.5	6.4	230	Rapidly progressive weakness. Death.
" 11	2.5	200	—	0	—	—	—	—	Depressed or excited at times, never in danger. Blood sugar ranged 84–113, untreated for 20 hours.
" 11 20 Hrs. later		200	1½	20	34	6.8	2.7	89	Weakness. Death in 11 hrs. after last glucose injection; blood sugar in this period 102–89 mg.

A further illustration of this difference with a smaller insulin dose (50 units) is shown in figure 2. A greater intensity of action of the regular insulin was shown by the much earlier onset of hypoglycemic attacks demanding glucose injections, and by the larger quantity of glucose thus required within the first 34 hours; but after that only the protamine animal needed glucose, and this need continued nine hours longer than in the rabbit which received regular insulin.

Fatalities, such as shown in table 3 and also others not tabulated, were escaped in only one instance, again illustrating the variability of individual rabbits. Following a dose of 200 units of protamine insulin subcutaneously on the side of the body (table 4), the most critical period was on the second

day, when there were 12 convulsive attacks. By continuous watching, it was possible to relieve each attack by a prompt subcutaneous injection of 20 c.c. of 10 per cent glucose (in saline) solution. This record is among those which prove that even a long series of violent convulsions, if each at-

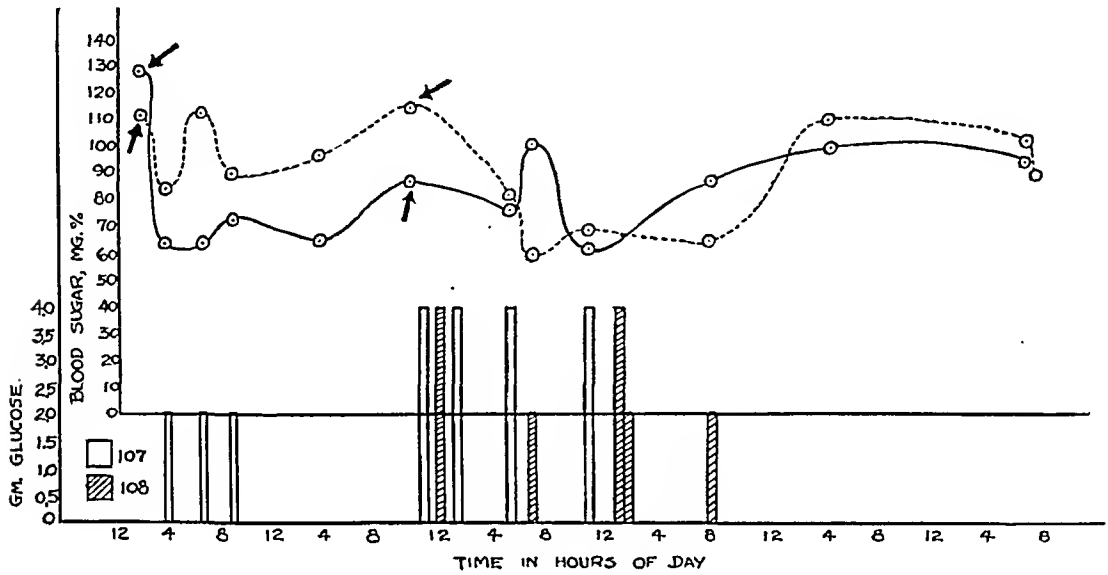


FIG. 2. Rabbit 107 (shown by continuous line) 200 units ordinary insulin, and rabbit 108 (shown by broken line) 200 units protamine insulin, intravenously, on two days. Arrows indicate time of injection.

TABLE IV  
One Subcutaneous Injection of Protamine Insulin; Fasting Throughout

Day of Experiment	Rabbit 23—200 Units		Rabbit 24—100 Units	
	Number of Convulsions	Glucose in 10% solution subcutaneously, gm.	Number of Convulsions	Glucose in 10% solution subcutaneously, gm.
1	5	10	11	14
2	12	24	12	15
3	5	10	3	3
4	8	16	3	3
5	10	20	2	2
6	8	16		
7	4	8		
8	2	4		
Total 8 days	54	108 gm.	Total 5 days, 31	37

tack is treated promptly, is not necessarily dangerous or seriously harmful. Numerous blood sugar analyses demonstrated the usual hypoglycemia in the attacks, hyperglycemia following the glucose injections, and considerable intervals of about 80 to 100 mg. per cent between. At the end, a period of

12 hours without convulsions was accepted as evidence that the effect of the insulin was ended. During the long fasting experiment, there were times when the rabbit was apparently willing to eat a little, but most of the time food was refused. At the end it was thin, weak and slightly hungry. Food was taken, first in small and then in large quantities, and full health and strength were rapidly regained. This period of eight full days represents a longer duration of effect of a single dose than has heretofore been reported.

TABLE V

Food and Glucose Administration after Single Protamine Insulin Injections in Rabbits

Rabbit no.	Insulin Subcut. Units	Food by Stomach	Glucose Subcut. gm.	Duration of Treatment. Hours	Final Blood Sugar mg. %	Result
1	200	400 c.c. 10% glucose by tube.	16	20	180	Progressive weakness. Death.
2	250	20 gm. bread voluntarily. 280 c.c. milk by tube.	2	18	192	No diarrhea or distention. Convulsions. Death.
3	250	450 c.c. milk and 5 gm. glucose by tube.	11	14	85	Slight diarrhea. Death with pneumonia.
4	250	300 c.c. 10% glucose by tube.	23	38	140	Progressive weakness. Death with pneumonia.
5	250	In first 24 hours, refused oats and bread; ate 220 gm. lettuce; given 50 c.c. milk and 100 c.c. 10% glucose by tube; slight diarrhea. Thereafter fasting.	59	104	45	Death probably from prolonged quiet hypoglycemia.

Rabbit 24 in table 4 illustrated a five-day effect of a single dose of 100 units of protamine insulin, given subcutaneously in the lower part of a hind leg. The blood sugar at death was 46 mg. Instead of convulsions, the hypoglycemia in this animal caused mostly a prolonged weakness. This was probably the cause of death, and the animal might perhaps have been saved by the use of larger quantities of glucose on the last three days. The site of injection of a large dose of insulin (body or leg) seems unimportant.

#### V. EXPERIMENTS WITH FEEDING

The failure of appetite after large doses of protamine insulin is still more marked than that observed after regular insulin. Even when a rabbit occasionally acts as if ravenously hungry, proffered food is eaten in only trivial quantity. In the hope of enabling rabbits to tolerate larger insulin doses, attempts were made to increase the intake by offering a variety of foods for voluntary eating and by tube feeding of milk or glucose, with the particular object of reducing the amount of glucose required subcutaneously. As shown in table 5, these attempts with protamine insulin were not as successful as those with ordinary insulin in the preceding paper.



All the rabbits died, though the result in rabbit 5 was apparently due to insufficient glucose. Later experiments have shown that this method can be developed so as to furnish more examples of the true maximum duration of effect of a single dose, such as was illustrated in table 4.

## VI. REPEATED SUBCUTANEOUS INJECTIONS OF REGULAR INSULIN

In addition to the examples in table 2, tables 6 and 7 show experiments with repeated injections of regular insulin, designed to ascertain to what extent the effects of protamine insulin can be thus imitated.

In table 6, the cat which received five injections of 50 units of regular

TABLE VI  
Cats and Rabbits—Repeated Injections of Regular Insulin Subcutaneously

Animal	Weight kg.	Insulin Dosage	Hours before 1st reaction	Carbohydrate			Total hours of glucose treatment	Final blood sugar mg. %	Result
				Fed gm.	Injected gm.	Total gm.			
Cat	2.2	5×50 units, at 5 hr. intervals	—		32		40	90	Severe prostration. Recovery.
Rabbit 1	2.0	1×50 units; starch and glucose by stomach tube; glucose subcut.	—	9.2	0	9.2	13	108	Slight weakness. Recovery.
Rabbit 1		1×50 units, 24 hrs. later	—	12	40	52	13	122	Apparently well for 13 hours; died during night when unwatched.
Rabbit 2	2.0	2×50 units, at 16 hr. intervals	2½		20		27	80	Progressive weakness; death. Initial erythrocytes 7.7, final 9.8 millions.

TABLE VII  
Rats—Repeated Injections of Regular Insulin Subcutaneously

Rat No.	Weight gm.	Insulin Dosage	Glucose injected Subcut.—gm.				Balance	Total	Total hr. of glucose treatment	Result
			In 1st 6 hrs.	In 2nd 6 hrs.	In 2nd 12 hrs.	In 3rd 12 hrs.				
1	150	3×20 units, 12 hr. intervals	0.8	0.7	1.1	1.7	3.0	7.3	54	Lived.
2	100	2×30 units, 16 hr. intervals	0.3	0.9	1.7	0.6	—	3.5	26	Death, probably from hypoglycemia.
3	195	4×5 units, 6 hr. intervals	0	0.5	1.0	2.8	—	4.3	33	Lived; weak and without appetite for several days.
4	180	8×1 unit, 2 hr. intervals	0.5	1.1	1.0	—	—	2.6	18	Died dyspneic, unconscious; blood sugar 80 mg.
5	190	7×½ unit, 2 hr. intervals	0.8	1.0	0.9	—	—	2.7	23	Death, probably from hypoglycemia.
6	160	12×¼ unit, 1 hr. intervals	0.6	1.5	1.1	—	—	3.2	15	Weakness. Death.

insulin at five-hour intervals became prostrated and required treatment for hypoglycemia for 40 hours. A continuous and sustained effect is neces-

sarily produced by the overlapping of these doses. Differences in the glucose requirement are probably accidental, and the prominent points of distinction seem to be two: (a) the total duration of effect of the multiple doses of regular insulin was much shorter than would undoubtedly be found with a single dose of 250 units of protamine insulin, if the animal could survive; (b) the full toxicity of a single large dose of either regular or protamine insulin was lacking, so that the animal was able to survive.

Rabbit 1 shows that a 50-unit dose, repeated after 24 hours, is more potent the second time than the first time, in respect to the total amount of glucose required for controlling the increased number of hypoglycemic attacks, and also in respect to duration. Death was evidently due to delayed hypoglycemia, after the mistake of stopping the treatment at 13 hours, in imitation of the first day.

Rabbit 2 illustrates a seemingly toxic effect of two 50 unit doses at an interval of 16 hours. The fatality seemed to be not accounted for by hypoglycemia, excessive glucose injections or excessive change in blood concentration. It was noticed in the previous paper that single doses above 100 units can be tolerated by rabbits.

Aside from the cumulative action of the insulin itself, certain harmful legacies from the early doses must be considered. The combination of insulin and glucose perhaps leaves an impoverishment in glycogen. A remaining hydremia due to glucose is illustrated by certain rabbits in table 4 of the preceding paper. It has not been possible, however, to arrive at any clear idea of the conditions under which multiple insulin doses are tolerated sometimes better and sometimes worse than single doses. Factors of both time and total amount are evidently concerned.

In table 7, the first three rats represent survival or merely accidental death with fractionated insulin doses. In each case the aggregate amount is far below what a rat can tolerate in the form of a single injection. The subdivision of this amount results in a marked prolongation of the effect and a correspondingly greater glucose consumption than with a single dose.

Rats 4, 5 and 6 show a tremendously greater efficiency of insulin, as measured by glucose consumption, when the doses are further subdivided into fractions as low as  $\frac{1}{4}$  unit. These results are suggestive in two ways.

First, it seems probable that if the dose of 10 or 15 units were divided into sufficiently small fractions and these injected hour by hour during several days, the full effect of this quantity of protamine insulin might be reproduced with regular insulin. This would confirm the idea that protamine insulin owes its special effect merely to the fact that a large portion of the dose remains for a long time unabsorbed, and the marked physiological action during this time results only from tiny fractions of the dose which enter into metabolism from hour to hour.

Second, another inference may be that the enormous doses of several hundred units are practically without physiological significance, except for furnishing a surplus insulin supply which may remain in the body as long as

several days. With these huge injections also, the effect may be due only to very small amounts which actually enter into metabolism from hour to hour, while the greater part may be destroyed merely as waste material. Clinicians have long known that insulin becomes more efficient unit for unit as it is divided into an increased number of doses. As already mentioned, the exaggeration of these conditions in laboratory animals facilitates study.

It is possible that either continuous intravenous infusion of insulin, or very frequently repeated fractionated subcutaneous doses, as already used by several authors (cf. Bischoff and Jemtegaard,<sup>7</sup> 1937), may be the only accurate method of studying the effects. As already mentioned, however, attention must be given to two points: (a) The very large insulin doses appear to have a specific toxic action, not found with smaller doses, even though the latter may seem to entail an equal glucose consumption. (b) It is difficult to see how very large doses can be studied by the intravenous or fractionated subcutaneous method, without the accumulation of a surplus in the tissues practically on a par with the single massive doses.

## VII. GLYCOGEN DEPOSITS

Unfortunately, only a few glycogen analyses could be performed by Mr. J. H. Rice. One of the rats represented in table 1, which died after 50 hours of glucose injections following a dose of 10 units of protamine insulin, was found to have 2.1 per cent of glycogen in the liver. Rabbit 5 in table 3, which died after repetition of 200 units of protamine insulin intravenously on the second day, having received 20 gm. of injected glucose in 34 hours, showed 3.1 per cent of glycogen in the liver, 0.9 per cent in the heart and 0.72 per cent in the leg muscles. Three other animals gave positive qualitative tests for liver glycogen.

All the results obtained can be harmonized under one general rule; namely, that animals dying from huge doses of regular insulin are nearly or completely glycogen-free; the controls after glucose alone contain glycogen; and those dying after small subcutaneous or larger intravenous injections of protamine insulin, when there has been heavy glucose dosage with a relatively small insulin influence, have contained more or less glycogen. It must be emphasized that the observations are too few to establish any such broad conclusion, and the supposed rule may be based only on accidents and may be disproved by adequate trial.

## VIII. CRYSTALLINE ZINC INSULIN

It seemed necessary to consider the possibility of some chemical basis for the peculiarities of protamine insulin, apart from the mere slowness of absorption. Therefore tests were made with insulin crystallized with zinc, as introduced by Sahyun in the laboratory of Frederick Stearns & Co. The great majority of clinical reports (cf. Barach<sup>8</sup>; Sprague and Rynearson<sup>4</sup>; Wilder and Wilbur<sup>6</sup>; and others up to 1937, also a series of papers<sup>10</sup> in

1938) agree that its duration of effect is much less than that of protamine insulin but distinctly greater than that of the ordinary commercial preparations of insulin, and this also has been the writer's experience with patients.

This difference can be clearly confirmed by taking advantage of the exaggerated conditions offered by tests in rats. In table 8, the effects

TABLE VIII  
Rats—Subcutaneous Injections of Stearns Crystalline Zinc Insulin

Insulin Units	Weight gm.	Glucose Injected Subcutaneously				Total Hours of Glucose Treatment	Result
		First 12 hours gm.	2nd 12 hours gm.	Re-maining Period gm.	Total gm.		
20	115	1.5	0.5	—	2.0	16	Prolonged hypoglycemia after last injection. Lived.
40	125	2.5	1.5	—	4.	24	Lived.
60	115	2.5	2.5	1.5	6.5	34	Weakness; death.
100	200	5.	3.5	—	8.5	36	Died 54 hours after last glucose injection.

of 20 and 40 units were decidedly longer lasting than with the same doses of ordinary (Lilly amorphous) insulin in the previous paper, and the apparent glucose equivalent per unit was correspondingly increased. The effects, however, were far shorter than those following protamine insulin; hence fasting rats readily survived after 20 to 40 units of the crystalline insulin, although they died with as little as 10 units of protamine insulin.

In subsequent experiments it has proved possible for rats to withstand 120 units or sometimes more of zinc crystalline insulin (Stearns) without hypoglycemic death, but such animals often lack appetite and die within one to three days later. These late deaths appear to be classifiable among the toxic effects of insulin. This question will be considered further in a subsequent paper, but according to the present evidence crystalline insulin is distinguished from amorphous insulin by toxicity as well as by duration of action. This greater toxicity is probably only a consequence of the more prolonged action. Accordingly, the toxicity as well as the duration of action of crystalline insulin is far less than that of protamine insulin.

#### IX. STORAGE SITE OF INJECTED INSULIN

There is a general belief that the absorption of insulin can be hastened and thus its effect accelerated by enlarging the area of absorption. The present work has not revealed such differences when the differences in injection have been slight. On the other hand, when the effects of large doses injected in one spot are compared with those following injections distributed over 10 or 15 areas, it has been shown that in the latter instance the

effects have been decidedly intensified and shortened. It is of interest that the shortening is more marked than the intensification, so that the glucose equivalent of each unit of insulin is diminished by wide distribution of the dose (thus approaching nearer to the intravenous results).

Other experiments were performed with injections of protamine insulin in the legs as near to the ankle as possible, followed by amputation above the knee. Table 9 shows that the effects can thus be cut short decisively. Life

TABLE IX  
Protamine Insulin Injections in Legs—Amputation

Animal No.	Weight	Prota- mine Insulin Dosage. Units	Hours of Treatment		Glucose In- jected, gm.		Result
			Before Ampu- tation	After Ampu- tation	Before Ampu- tation	After Ampu- tation	
Rat 1	150 gm.	20	36	27	8.8	0.4	Weakness probably due to glucose. Death.
" 2	130 "	20	17	17	3.5	1.0	Weakness ; death.
" 3	220 "	15	9	12	1.6	0.8	Lived.
" 4	120 "	20	12	3	2.5	0.8	Lived.
" 5	225 "	60	20	—	3.8	0	Lived.
" 6	170 "	100	62	—	6.5	2.0	Also drank considerable glucose before amputation. Lived.
Rabbit 1	2 kg.	200	9.	12.	15.	8.	Weakness and death without hypoglycemia.
" 2	2 kg.	200	12	—	8.	1.	Lived. Lively.

is thus saved even after hopelessly fatal doses—up to 100 units of protamine insulin in rats or 200 units in rabbits; also after very long periods, up to a maximum of 62 hours from the time of injection in rats. Generally the injection of a little glucose has been necessary for a short time after amputation, because of either convulsions, weakness, or hypoglycemia as revealed by analyses. In the large strong rat 5, survival was obtained without any glucose after amputation, though the protamine insulin was in the large dose of 60 units and the operation was 20 hours after the injection.

Inspection of the injected area in rats after 20 hours or more showed entire absence of edema or inflammatory signs and strictly normal naked-eye appearances. The complete absorption of the injected fluid seemed obvious. cursory examination of stained microscopic sections has also thrown no light upon the location or state of the retained insulin.

It will be noticed that these results were directly opposite to those described with regular insulin in the preceding paper. Because of the smaller volume of the injection, and the longer time, the absorption of visible fluid was much more complete in the case of the protamine insulin; nevertheless the biologically demonstrable local retention of insulin continued much longer.

The extracellular retention of a combined form of insulin for 62 hours or possibly for still longer periods (e.g. the effects for eight days in the rabbit in table 4) may suggest still greater care in theorizing concerning the limits of the time during which the organism can retain residues of insulin in unknown combinations intracellularly.

There is also an apparent dilemma, as follows: (a) It may be assumed that the greatly prolonged effect (three to five days for 10 to 20 units in rats, eight days for 200 units in rabbits) may be due to a slower absorption than in man. In this case protamine insulin seems to stand alone among all known drugs. (b) It may on the other hand be assumed that the absorption is equally slow in man; i.e., that residues from all protamine insulin doses are still being absorbed five to eight days after injection, and the small animals merely serve as a more delicate indicator because of their sensitiveness to traces of insulin too small for perceptible effects in man. It is necessary to reconcile this assumption with the high tolerance of the animals (especially with spontaneous eating) for regular insulin. Some simple solution would presumably have been arrived at if the experimental program could have been completed. The second assumption seems more probable, especially in view of the results in table 7; and if it be correct that residues from small or large injections are still being absorbed after five to eight days, the cumulative action of protamine insulin receives even a more ample explanation than could have been anticipated from the clinical findings.

### CONCLUSIONS

1. The tolerance of rats for protamine zinc insulin with spontaneous eating is much lower than for regular insulin, i.e., below 60 units. The loss of appetite, and also the death of rats, rabbits and cats with high doses, seem to show a greater toxicity of protamine than of regular insulin.

2. Under fasting with parenteral glucose injections, the tolerance of average cats and 2-kg. rabbits is below 200 and perhaps below 150 units of protamine insulin. The tolerance of average rats is below 15 units; exceptionally large rats may tolerate 20 units or perhaps more.

3. The duration of the hypoglycemic effect of protamine insulin in animals is greater than has ever been reported before, namely up to five days in rats and eight days in rabbits.

4. This prolonged action of protamine insulin cannot be imitated satisfactorily with repeated large injections of regular insulin, without running into doses enormously higher than the protamine insulin dose. Comparative calculations of the glucose equivalents are thus made irrational. The closest imitation is afforded by doses of only a fraction of a unit of regular insulin repeated at very short intervals.

5. Though small doses of protamine insulin elicit nearly the same rate of glucose consumption as huge doses of regular insulin, they apparently do not have the same "toxic" action. Also a few analyses suggest that they do not have the same effect in depleting glycogen.

6. Comparison with crystalline zinc insulin, which is intermediate in rate of absorption between regular and protamine insulin, gives intermediate results in influence upon glucose consumption and also as to toxicity.

7. Amputation experiments prove that the delayed action of subcutaneously injected protamine insulin is due to retention at the site of injection, for periods tested up to 62 hours.

8. The findings in animals are similar to those in man, but exaggerated in degree. They necessitate the conclusion either that the absorption rate differs in different species, or that active residues of protamine insulin remain in the body for longer periods after injection than heretofore supposed.

9. Since the writer's first publication in 1913,<sup>9</sup> there has been no opportunity of investigating the diuretic action of glucose. The hypothesis of colloid-combined blood sugar in the normal, and free sugar in the diabetic, seems to have been disproved by direct physicochemical tests. It is also evident that the writer's intravenous glucose injections, likewise the subsequent ones of Woodyatt and others, were diuretic only by reason of the injected fluid and of fluid withdrawn osmotically from the tissues, the diuretic agent being the water or saline and not the glucose. In general, hyperglycemia in the normal organism is accompanied not by polyuria but by hydremia, unless the latter is prevented by excessively concentrated solutions. In mild diabetes the urine volume is variable. In severe uncomplicated diabetes, polyuria with heavy glycosuria is the rule; hydremia is unknown and the extreme diuresis may even concentrate the blood. This contrast still seems to represent a fundamental unexplained phenomenon of diabetes, which subsequent investigators have missed even after it had been plainly pointed out. Whether there is this supposed significance or not, and whether the large insulin doses modify this effect of glucose or not, could not be decided under the conditions of the present work; but these observations confirm the actual facts described in 1913, even to the extent of far more extreme hydremia than was then claimed.

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# CASE REPORTS

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## ANGINA PECTORIS AS A PREDOMINATING SYMPTOM IN SPONTANEOUS HYPOGLYCEMIA \*

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WHILE the general symptomatology of hyperinsulinism has been known since Harris<sup>1</sup> first recognized the syndrome in 1924, symptoms referable to the gastrointestinal tract, and vague generalized symptoms of varying degrees of severity as are usually observed in the psychoneuroses and in vasomotor disturbances have been the main features described.

We wish to report two cases which have come under our observation in which the predominating symptom was angina pectoris.

### CASE REPORTS

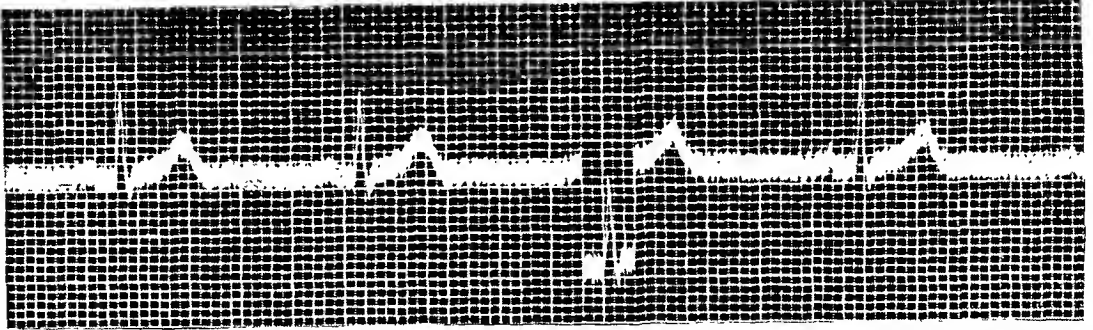
*Case 1.* A male, 42 years of age, gave a two year history of attacks of substernal pains radiating to both shoulders, coming on with exertion or excitement and requiring complete rest for relief, lasting a variable time (2 or 3 to 10 minutes) and always occurring before meals. There was usually an associated empty feeling in the head, cold sweat and pallor. He was a heavy smoker and had had a chronic cough for many years. Physical examination showed an increase in the aortic width, slight increase in the total cardiac diameter and a rough aortic systolic murmur. The liver was not enlarged; there was no edema. The dorsalis pedis pulses were palpable. The blood pressure was 130 mm. mercury systolic over 95 mm. diastolic. Roentgen-ray examination of the gastrointestinal tract was negative. The basal metabolic rate was normal. The electrocardiographic tracings showed minimal changes (figure 1). The blood sugar tolerance curve showed 59 mg. (fasting), 118 mg. (1 hour); 94 mg. (2 hour); 72 mg. (3 hour); 54 mg. (4 hour). Between the third and fourth hours of the test, the patient complained of marked discomfort and substernal distress, there was a marked pallor and a cold sweat. After the last specimen of blood was taken, the administration of glucose brought prompt relief.

*Case 2.* Male, 39 years of age, with a one year history of attacks of precordial pains, variable in character and lasting a few minutes, radiating to the left shoulder and arm, coming on with exertion or excitement only when he was hungry, rarely when at rest, but then also when hungry. He was a heavy smoker and had had a chronic cough for many years. Physical examination revealed slight sclerotic changes of the retinal vessels; slight increase in the aortic width; the heart was not enlarged; the liver was not palpable; there was no edema; the dorsalis pedis pulses were palpable. The blood pressure was 140 mm. mercury systolic over 90 mm. diastolic. The urine examination was negative. Roentgen-ray examination of the gastrointestinal tract was negative. The basal metabolic rate was normal. The electrocardiographic tracings showed minimal changes (figure 2). The blood sugar tolerance curve was 64 mg. (fasting); 115 mg. (1 hour); 80 mg. (2 hour); 58 mg. (3 hour); 42 mg. (3 hour)

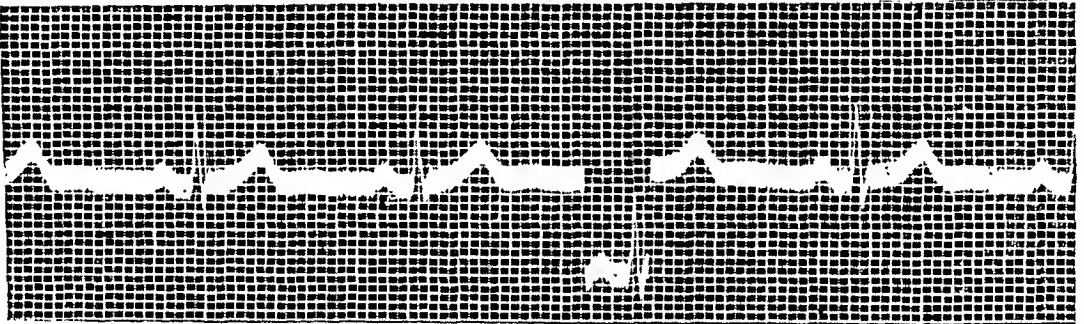
\* Received for publication March 29, 1938.

From the M. A. Rabinowitz Medical Service of the Jewish Hospital of Brooklyn.

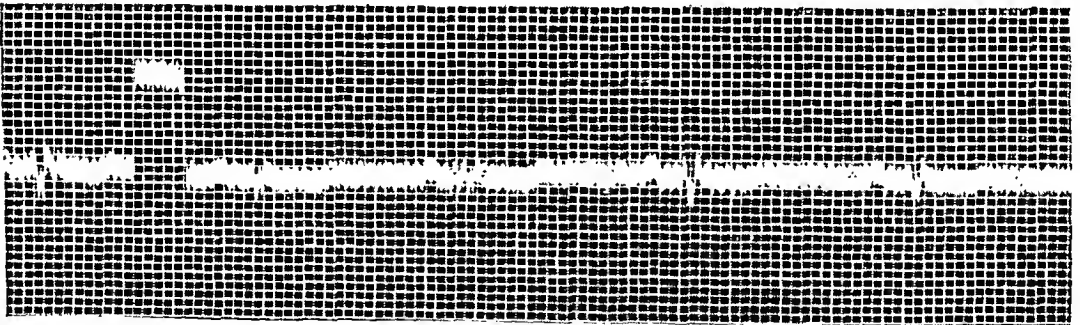
Lead I



Lead II



Lead III



Lead IV

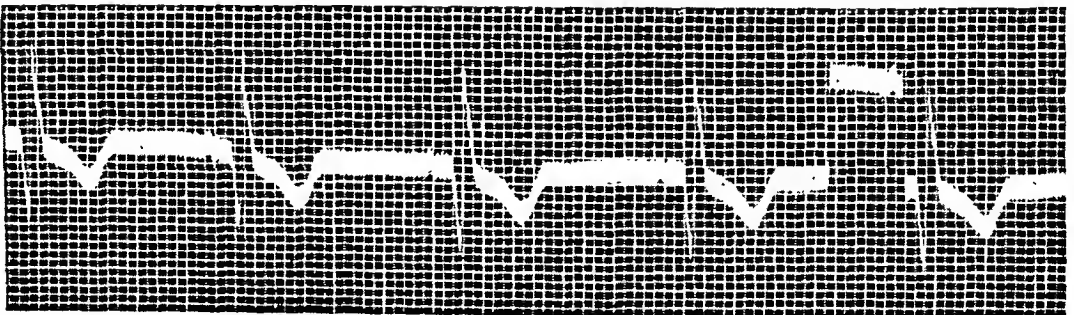
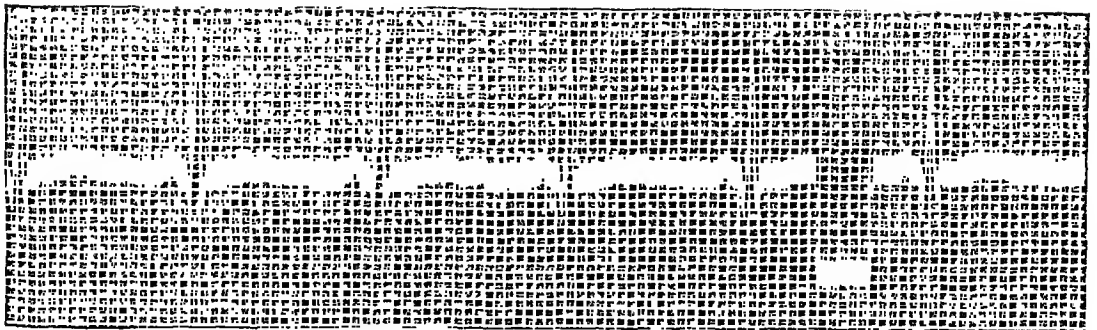
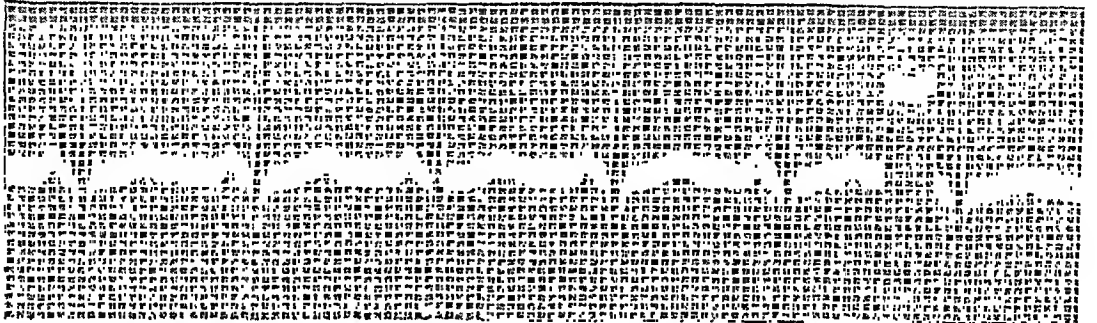


FIG. 1. Electrocardiograms of Case 1.

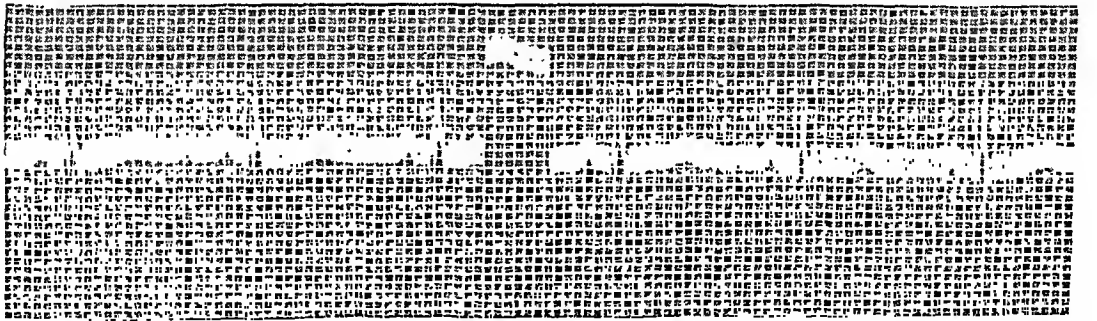
Lead I



Lead II



Lead III



Lead IV

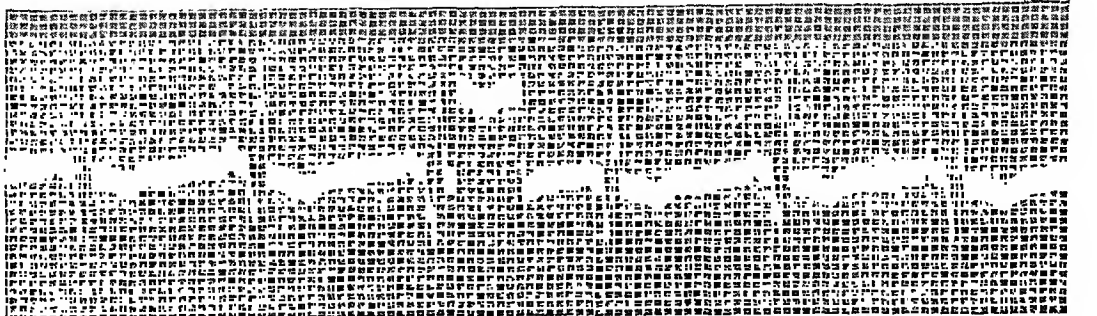


FIG. 2. Electrocardiograms of Case 2.

and 45 minutes). An excruciating attack of precordial pain necessitated terminating the test 15 minutes ahead of time and again the administration of glucose afforded prompt relief.

### DISCUSSION

Harris<sup>1, 2, 3, 4</sup> considered the clinical type of hypoglycemia to be due to excessive insulin secretion by the islands of Langerhans of the pancreas and developed the conception of hyperinsulinism as a disease entity as definite as the opposite condition of hypoinsulinism or diabetes mellitus.

While cases of pancreatic hyperinsulinism have been reported in which on exploration islet-cell tumors have been found (Graham and Womack,<sup>5</sup> Wilder, Allen, and Power<sup>6</sup>), in the majority of cases, the pancreas appears to be apparently normal and these cases must be grouped with diabetes and other functional disorders of the endocrine system.<sup>7</sup> Various etiologic factors have been suggested such as an inheritable constitutional predisposition, low grade pancreatic infection in association with duodenal ulcer, cholecystitis and cholelithiasis (Harris), and various precipitating factors such as excessive ingestion of carbohydrates, infection, trauma, fatigue, exhaustion, and nervous and emotional disturbances. There may be an association of hyperinsulinism with other endocrine lesions such as adrenal or pituitary tumor or hyperthyroidism.

Harris, in discussing the symptomatology, considered several types. The mild type where the attack consists of weakness, anxiety, pallor, especially about the lips, sweating and trembling occurring with hunger and relieved by the ingestion of sugar. The moderately severe type where there is profuse sweating, palpitation, prostration, more marked anxiety, mental lapses, periods of unconsciousness, and spasms of isolated groups of muscles (attacks resembling petit mal) also occurring with hunger and relieved by ingestion of sugar. The severe type where there are recurring attacks of unconsciousness, convulsions, narcolepsy, associated perhaps with major hysteria or actual psychosis (attacks may resemble grand mal epileptic seizures). The type where abdominal pain is the main feature, often suggesting an acute surgical abdomen, here again attacks occurring with hunger and relieved with the ingestion of sugar.

In our cases, while there were features of the other types, the predominating symptom and the one for which they sought medical aid was angina pectoris. In both of our cases, the relationship of the angina to hunger was brought out only on direct questioning and in both the relief of the attack with the ingestion of sugar was prompt.

The characteristic blood sugar tolerance curve shows unusually low readings throughout or a normal peak with subsequent depression of figures far below that observed in normal cases. Harris brought out that "one fasting blood sugar determination or one glucose tolerance test is not always sufficient because there seem to be periods when the patient with hyperinsulinism will show normal readings. The element of mental and physical fatigue affects both blood sugar levels and in making the tests the patient should not be permitted to lie down. In some cases, the blood sugar levels may remain normal for the first four hours and fall to very low levels in the fifth and sixth hours."

While ingestion of sugar will control the immediate attack, it also stimulates insulin production, so that a large dose of sugar may provoke a more severe attack several hours later. Harris and others have advocated a low carbohydrate,

moderate protein and high fat diet, providing approximately 1 to 2 gm. carbohydrate, 1 gm. protein and 2 to 2.5 gm. fat per kilo of body weight per day divided into six to eight portions. More carbohydrates must be given in the more severe types. Frequent blood sugar determinations should be made in the regulation of the diet.

Both of our cases presented strikingly similar features. The patients were males, around 40 years of age, short, stocky with a tendency to obesity. They were heavy smokers and though the changes on the electrocardiograph tracings were negligible, they had some evidence of early sclerotic vascular changes. The blood sugar tolerance curves were characteristic in both cases showing a low fasting sugar, a peak below the average normal and a rapid drop to subnormal figures. The pains, in both cases, were substernal or precordial in type and while they occurred with exertion or excitement, there was a definite relationship to hunger and the ingestion of glucose brought prompt relief. Both cases were treated with diets similar to those discussed above and have remained free from attacks.

#### SUMMARY AND CONCLUSIONS

The subject of spontaneous hypoglycemia is briefly discussed and two cases in which angina pectoris was the predominating symptom are reported. The similarity of the clinical picture, the characteristic sugar tolerance curves and the prompt response to dietary measures are discussed. The importance of inquiring into the association of anginal pains with hunger, even though the attacks are also definitely related to effort or excitement, is stressed.

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## OCCLUSIVE ARTERIAL DISEASE OF THE LOWER EXTREMITIES ASSOCIATED WITH LIPEMIA AND XANTHOMA TUBEROSUM\*

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IN the past two years two patients have been observed at the clinic who presented the clinical picture of occlusive arterial disease of the legs, xanthoma tuberosum of the skin and marked lipemia.

The first patient was a man, aged 46 years, of Welsh and French ancestry, who apparently always had enjoyed good health. He complained solely of typical intermittent claudication of the calves of both legs of seven years' duration which had become progressively more severe. He smoked an average of 25 to 30 cigarettes a day; he gave no history of phlebitis, pain or trophic changes in the toes, or any symptoms referable to the upper extremities. Nodular yellow cutaneous lesions in the region of the elbows and of the knees had been present for 12 years and scattered, small, yellowish papulo-squamous lesions of the trunk had been present for six years. His past history and family history were negative.

The nodular cutaneous lesions were typical of xanthoma tuberosum. Pulsations were absent in the popliteal, posterior tibial and dorsalis pedis arteries of both legs, were slightly diminished in the left femoral artery and were normal in the right femoral, and both brachial, radial and ulnar arteries. There was definite pallor of both feet on elevation of them and slight reactionary rubor of the toes on dependency. The patient was of normal build and weight. General physical examination otherwise gave negative results. No abnormalities were seen in the ocular fundi. Blood pressure, urine, concentration of hemoglobin and number of erythrocytes and of leukocytes were normal; roentgenographic examination of the thorax and Kline test of the blood gave negative results. The electrocardiogram was negative. Roentgenographic examination of the thighs and legs revealed no evidence of calcification of the arteries. A glucose tolerance test gave normal results, the maximal value for blood sugar being 146 mg. per 100 c.c. and no glycosuria being induced. The value for blood cholesterol was 667 mg. per cent, that for fatty acids was 1554 mg. and that for total lipoids was 2221 mg.† Intermittent claudication was produced in the calves of both legs by employment of a standard test in which the patient walked at the rate of 120 steps per minute. The symptoms appeared in from 6 minutes and 38 seconds to 7 minutes and 13 seconds on three successive days. This patient was given a diet low in content of fat and cholesterol and was observed at intervals during a period of 21 months. Subsequent determinations of the lipoids of the blood are given in table 1. During the period mentioned, the patient's general health remained good. At the last examination pulsations were unchanged from those observed at the previous examinations; postural changes in color had disappeared and the claudication did not develop until 20 minutes after the walking test was begun.

The second patient was a woman, aged 49 years, of English and Irish ancestry, who presented herself at the clinic and gave a history of numerous symptoms of a number of years' duration: migrainous headaches, fatigability, nervousness, attacks of vertigo, shortness of breath on exertion, palpitation of the heart, gaseous indigestion, intermittent diarrhea and failure of mental concentration. In addition, one com-

\* Read before the meeting of the Central Society for Clinical Research, Chicago, Illinois, November 5, 1937.

† All determinations of the lipoids of the blood mentioned in this report were done on plasma. The determinations of concentration of cholesterol, of fatty acids, and of total lipoids were made by the Bloor method, that of lecithin by the Whitehorn method.

TABLE I  
Values for Blood Lipoids in Milligrams per 100 c.c., Case 1

Date	Total cholesterol	Cholesterol esters	Lecithin	Fatty acids	Total lipoids
9-19-35	667			1554	2221
10-18-35	476			1283	1759
12-14-35	463			1267	1730
2-29-36	463			1003	1466
5-26-36	555		510	1286	1841
8- 5-36	476	320	520	1310	1786
10-11-36	476		478	1389	1865
2- 8-37	340	260	390	935	1275
6- 4-37	407		378	666	1073

plaint was of pain in the calves of both legs induced only by walking and rapidly relieved by standing still. This had been noted for six months. The patient also stated that yellowish, nodular lesions of the skin of the elbows, knees, feet and dorsal surfaces of the hands had been present for 10 years.

The lesions were typical of xanthoma tuberosum. Pulsations were absent in both posterior tibial arteries, were definitely reduced in the right dorsalis pedis artery and were barely palpable in the left dorsalis pedis artery; pulsations were present and normal in the popliteal, femoral, brachial, radial and ulnar arteries. No postural changes of color were noted. General physical examination was otherwise objectively negative. Nothing abnormal was noted in the ocular fundi. Blood pressure, urine, concentration of hemoglobin and number of erythrocytes and of leukocytes were normal; the Kline test of the blood and roentgenographic examinations of the thorax, legs and thighs gave negative results. The concentration of blood sugar (fasting) was 79 mg. per 100 c.c.; the basal metabolic rate was minus 7 and the electrocardiogram was normal. Examination of the blood lipoids gave evidence of marked lipemia; the concentration of cholesterol was 657 mg. per cent, that of fatty acids 1018 mg. and that of total lipoids 1675 mg. Biopsy of one of the nodular cutaneous lesions on the elbow demonstrated a histologic picture typical of xanthoma tuberosum. Intermittent claudication was produced in the calves of both legs by employment of the standard walking test after 2 minutes and 51 seconds. This patient was also given a diet low in content of fat and cholesterol. Subsequent determinations of the lipoids of the blood are given in table 2. During the period of observation symptoms of intermittent claudication and pulsations of the arteries of the legs remained unchanged.

It will be noted that although there was a definite reduction in concentration of lipoids in the blood in both cases during the period of dietary treatment, the concentration of lipoids did not drop to a level within normal limits. The diets contained approximately 30 gm. of animal fat a day. Attempts were made to give these patients diets which contained less than 2 gm. of animal fat a day and very little cholesterol. These diets were tolerated very poorly. In both cases marked fatigability and weakness of muscles developed but these symptoms may



TABLE II

Values for Blood Lipoids in Milligrams per 100 c.c., Case 2

Date	Total cholesterol	Cholesterol esters	Lecithin	Fatty acids	Total lipoids
4-14-36	657			1018	1675
4-23-36	595			1050	1645
4-29-36	667			766	1433
9- 5-36	333			787	1120
12-24-36	416			666	1082
6-18-37	416	298	402	661	1077
6-30-37	396	278	402	880	1276

have been owing to deficiency of the diet in some factor other than fat and cholesterol. Finally, the diets were discontinued voluntarily by both patients and the diets originally used were resumed.

The association of xanthoma tuberosum of the skin with increased concentration of blood lipoids has been emphasized recently by Montgomery and by Montgomery and Osterberg, who found definitely high values in almost all of the cases they studied. The chief purpose of this paper is to call attention to the possible relationship between the hyperlipemia and hypercholesterolemia on the one hand and the occlusive arterial disease on the other. In the absence of pathologic studies of the blood vessels, the nature of the arterial lesion can only be inferred. The two common chronic occlusive arterial diseases of the legs are thrombo-angiitis obliterans and arteriosclerosis obliterans. Although blood lipoids may be slightly elevated when either of these conditions is present, their concentration does not approach the high levels observed in the two cases herein reported (table 3). The onset of intermittent claudication in the fourth or fifth

TABLE III

Plasma Lipoids in Occlusive Arterial Disease of the Legs

	Cholesterol		Fatty acids		Total lipoids	
	Range	Average	Range	Average	Range	Average
Normal	160-200	180	200-250	225	500-550	525
Thrombo-angiitis obliterans (Roth and Allen, 36 cases)	102-273	192	194-603	377	360-871	563
Arteriosclerosis obliterans, 12 cases	191-321	278	324-593	432	515-791	691
Case 1, this report	667		1554		2221	
Case 2, this report	657		1018		1675	



decade of life always engenders the suspicion that thrombo-angiitis obliterans is present, but neither of the patients whose cases have been reported had experienced superficial phlebitis or involvement of the arteries of the upper extremities which, when present, are distinguishing characteristics of thrombo-angiitis obliterans; also, thrombo-angiitis occurs very rarely among women. Typical arteriosclerosis obliterans of the legs rarely is seen before the age of fifty, but it does occur. The absence of evidence of calcification of the arteries in the roentgenograms does not preclude the presence of such a lesion. The most likely possibility is that the arterial lesions were premature extensive atheromatous formation accompanied by a minimal degree of degenerative change in the medial coat. It is well known that atheromatous lesions have some of the features of xanthoma tuberosum and usually contain rather large amounts of fat and cholesterol. In 1936, Ochsner and Conner reported a case in which the values for blood lipoids were high (cholesterol 667 mg.; fatty acids 1971 mg.) and the patient died of coronary occlusion at the age of 55 years. Diabetes mellitus and xanthoma tuberosum were not present. Necropsy disclosed extensive atheromatosis of the aorta and of many large arteries; the atheromas contained an abnormally large amount of cholesterol and lipid material.

Association of excessive formation of atheromas in the heart and blood vessels with xanthoma of the skin was noted by Fagge in 1873, and by Lehzen and Knauss in 1889. A peculiar type of atheromatosis, characterized by numerous foam cells, in association with xanthomatosis of the skin and with diabetic coma was reported by Oppenheimer and Fishberg in 1925. Montgomery reported that in more than 25 per cent of his series of cases of xanthoma tuberosum, clinical evidence of coronary sclerosis and angina pectoris was present.

There is certainly reason to believe that association of the hyperlipemia and hypercholesterolemia with occlusive lesions of the arteries as noted in the cases I have described is more than incidental. Ignatowski, in 1908, observed atheromas in the aortas and large arteries of rabbits after they had been fed milk, and egg yolks. Similar lesions were produced by Anitschkow and Chalataw by feeding rabbits pure cholesterol. This work was confirmed by Bailey in 1916 and by Leary in 1934 who have stated that the lesions were identical with those of atheromatosis as observed in human subjects. It is interesting that the xanthomatous lesions of the skin appeared five years before the intermittent claudication in my first case and more than nine years before, in my second case, and it can be assumed that concentration of the blood lipoids was, at least, somewhat increased during these periods.

It would seem that there is sufficient reason to attempt to reduce the lipemia in these cases. As noted, this reduction was obtained partially in both cases by means of the diets low in content of fat. Coincidentally with the reduction in concentration of lipoids of the plasma the symptoms and signs of the vascular disease improved in one instance but remained stationary in the other. There has been no clinical evidence of further vascular occlusion.

Finally, I wish to emphasize Montgomery's statement that peripheral arterial disease may occur in association with xanthoma tuberosum. As this type of xanthomatosis may be asymptomatic, patients who have peripheral arterial disease should be examined carefully for evidence of xanthomatous lesions and patients who have xanthomatous lesions should be examined carefully for evidence of peripheral arterial lesions.

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## EDITORIAL

### *SERUM LIPASE IN THE DIAGNOSIS OF THE DISEASES OF THE PANCREAS*

Until 1932, investigators of diseases of the pancreas used the concentration of that fat-splitting enzyme in the serum which is capable of splitting simple esters (esterase) in the diagnosis of pancreatic disease; but the results were too variable to be of great value. In 1932, Cherry and Crandall<sup>1</sup> re-examined the problem of fat-splitting enzymes in the serum, finding that the activity of the esterase as measured by hydrolysis of ethyl butyrate or tributyrin was affected in one of three ways: it was increased, decreased, or was not changed following experimental ligation of the pancreatic duct of dogs. They therefore concluded that the esterase did not respond according to any definite pattern.

This explained the discordant results obtained by the investigators who had used simple esters as substrates in the study of pancreatic lipase in the blood. In contrast to the variability of the influence of experimental ligation of the pancreatic duct on the values for ester-splitting enzymes in the serum, these authors showed that an enzyme capable of splitting olive oil (lipase) appeared regularly in the blood stream of dogs in large amounts following the same procedure. Hence, the appearance of this enzyme in the blood made possible the development of a promising test for the detection of pancreatic disease.

The degree of lipase activity of the serum was determined by the amount of olive oil hydrolyzed by a given quantity of serum in a given period of time. The value is expressed in terms of cubic centimeters of twentieth-normal sodium hydroxide used to neutralize the fatty acids liberated by 1 c.c. of serum. Cherry and Crandall<sup>1</sup> found that an olive-oil-splitting lipase was absent from the blood of dogs.<sup>1</sup> They also found that the sera of only six of the 146 dispensary patients contained even a trace of olive-oil-splitting enzyme. Comfort and Osterberg, on the contrary, reported that, using the method of Cherry and Crandall, they observed an olive-oil-splitting lipase which was almost constantly present in small amounts in the sera of persons free from abdominal disease who were examined at The Mayo Clinic. Comfort reported that the range for values of lipase in the serum in persons free from abdominal disease was between 0.2 c.c. and 1.5 c.c. twentieth-normal sodium hydroxide per 1 c.c. of serum. The most frequent values were 0.6, 0.7, 0.8, and 0.9 c.c. This discrepancy in normal values undoubt-

<sup>1</sup> CHERRY, I. S., and CRANDALL, L. A., JR.: The specificity of pancreatic lipase: its appearance in the blood after pancreatic injury, *Am. Jr. Physiol.*, 1932, c, 266-273.

<sup>2</sup> COMFORT, M. W., and OSTERBERG, A. E.: Lipase and esterase in the blood serum; their diagnostic value in pancreatic disease, *Jr. Lab. and Clin. Med.*, 1934, xx, 271-278.

<sup>3</sup> COMFORT, M. W.: Serum lipase; its diagnostic value, *Am. Jr. Digest. Dis. and Nutrition*, 1937, iii, 817-821.

edly depends on slight differences in technic and should disappear as the method becomes standardized.

Elevated values for lipase in the serum occur regularly following experimental ligation of the pancreatic duct in dogs<sup>1</sup> and also after experimentally produced pancreatitis.<sup>4</sup> Experimental ligation of the pancreatic duct always has been followed within a few hours by a rapid rise in values for the lipolytic activity in the serum, which returns to normal in about ten days, even though the ligatures are intact and the obstruction is complete. Apparently, the glandular tissues cease to secrete after a certain length of time; but secondary rises in concentration may occur later. Similarly, pancreatitis experimentally produced by the injection of bile into the pancreatic ducts of dogs has been uniformly followed by a rise in values for serum lipase. The concentration returns to normal levels as the inflammation subsides; this usually occurs within seven to ten days after this procedure. The elevation of values following both experimental procedures is presumably the result of reabsorption, although there is evidence tending to indicate that pancreatic enzymes may be secreted into the blood stream.<sup>5, 6, 7</sup> The rapidity of the occurrence of elevated values following these experimental procedures and the definite limitation of the duration of elevation of values will be found especially significant in the interpretation of the behavior of values for lipase in clinical conditions.

Substantial clinical experience with the stimulation of the activity of lipase in the serum as a test of pancreatic disease has also been reported.<sup>2, 3</sup> Values for lipase up to the amount of 10 c.c. of twentieth-normal sodium hydroxide per 100 c.c. of serum have been reported when disease of the pancreas has been present. Values for serum lipase were elevated in 15 of 41 cases (36 per cent) in which malignant disease of the pancreas was demonstrated at operation and in three of five cases of carcinoma of the ampulla of Vater.<sup>2</sup> Such a low percentage of elevated values accompanying malignant disease of the pancreas may be accounted for by the fact that elevated values are found only when the carcinoma has obstructed the pancreatic ducts and when the determinations are carried out during the time that the gland is actively secreting into an obstructed duct. It is clear from these figures that a normal value for serum lipase does not exclude the possibility of malignant disease of the pancreas.

Inflammatory disease of the pancreas, however, presents a much different picture.<sup>3</sup> Elevated readings for serum lipase could be found in 95 per cent

<sup>1</sup> BAXTER, HAMILTON, BAXTER, S. G., and MCINTOSH, J. F.: Variations in the level of serum lipase in experimental pancreatitis, *Am. Jr. Digest. Dis. and Nutrition*, 1938, v, 423-425.

<sup>2</sup> ANTROPOL, WILLIAM, SCHIFRIN, ARTHUR, and TUCHMAN, LESTER: Blood amylase response to acetylcholine and its modification by physostigmine and atropine, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxii, 383-385.

<sup>3</sup> FRIEDMAN, IRVING, and THOMPSON, W. R.: Induced and spontaneous changes in blood amylase particularly in relationship to the pancreas; an experimental study, *Ann. Surg.*, 1936, civ, 388-402.

<sup>7</sup> TUCHMAN, LESTER, SCHIFRIN, ARTHUR, and ANTROPOL, WILLIAM: Blood amylase response to acetyl-beta-methylcholine chloride in pancreatectomized dogs, *Proc. Soc. Exper. Biol. and Med.*, 1935, xxxiii, 142-144.

of cases of subacute or acute pancreatitis, provided the readings were taken during the acute phase of the inflammation or within the first few days of the onset of the disease. Elevated values have been obtained occasionally as late as 21 days after the initial attack, but in these cases there was clinical evidence of exacerbation of the inflammation. The lone exception to the general rule that elevated values occur during the acute phase was found in a case of pancreatic necrosis, the normal value in this instance being attributed to widespread destruction of the architecture of the pancreas and absence of functioning pancreatic tissue. Elevated values will apparently be found with great regularity in subacute or acute pancreatitis, provided the acute process has not subsided and that some functioning pancreatic tissue remains intact. Elevated values have not been encountered after the acute process has subsided or in the presence of chronic atrophic pancreatitis.

Individual determinations of the activity of lipase in the serum appear to furnish an efficient test for acute or subacute pancreatic disease, but they are of considerably less value in testing for the presence of malignant disease of the pancreas. It must be emphasized, however, that elevated values do not distinguish the types of pancreatic disease present in the individual case. This point must be determined by the clinical and physical findings. If values are repeatedly determined and curves are constructed therefrom, the type of curve resulting may prove somewhat distinctive of the type of pathologic condition present. If values for serum lipase rise rapidly following an acute attack of upper abdominal pain and then fall rapidly to normal levels, the physician may safely assume that such behavior favors the presence of pancreatitis. If the values for lipase in the serum in the presence of a painless jaundice are increased and remain at a fairly constant level, carcinoma of the head of the pancreas is probably present.

Elevated values for lipase suggest the presence of pancreatic disease in a great majority of cases. The fact that elevated values do not necessarily imply the presence of pancreatic disease in cases of obstructive jaundice must be considered, however, for it has been shown that experimental ligation of the common bile duct is followed by a marked rise in values for lipase.<sup>8</sup> Moreover, Comfort has reported such elevated values in 19 cases of jaundice, most of which were caused by obstruction of the duct by stone or stricture. While the pancreas was not examined by the surgeon in these 19 cases and while the pancreas cannot be excluded as a cause of the elevated values, the additional possibility that the obstruction of the common bile duct was responsible for the elevations of values in these cases must be thought of. But, on the contrary, Comfort's report that in 26 cases of obstructive jaundice caused by carcinoma of the head of the pancreas, and in 62 cases of jaundice (most of which were obstructive in type and the result of stone or stricture of the common bile duct) normal values were obtained, is strong evidence that obstruction of the duct rarely will be the cause of elevated

<sup>8</sup> CRANDALL, L. A., JR., and CHERRY, I. S.: The regulation of blood lipase and diastase by the liver, *Am. Jr. Physiol.*, 1931, xcvi, 515-516.

values for lipase and so lead to an erroneous diagnosis of pancreatic disease. Since it is possible that these elevations are sometimes the result of obstruction of the common bile duct, elevated values for lipase in cases of obstructive jaundice must be interpreted with this possibility in mind until the chance of error from this source is more fully determined.

It seems safe, therefore, to conclude (1) that elevated values for lipase in the serum point with a high degree of certainty to the presence of benign or malignant disease of the pancreas associated or not associated with acute or chronic disease of the gall-bladder, with cholangitis, with choledocholithiasis or with stricture of the common bile duct, and (2) that while elevations of values for lipase in the serum are probably not specific for the presence of pancreatic disease, the test may be used to advantage in the diagnosis of malignant disease of the pancreas or acute or subacute pancreatitis. Certainly, its diagnostic possibilities are so attractive that further clinical application of the test, carefully controlled by pathologic studies of the pancreas at the operating table, is highly desirable.

M. W. C.

## REVIEWS

*The Spectacle of a Man.* By JOHN COIGNARD, M.D. 252 pages; 21 × 14 cm. Jefferson House, Inc., New York City. 1937. Price, \$2.50.

This book is an attempt by a psychiatrist, under a pseudonym, to show the changes in his patient's social relationships which occurred during a period of psychoanalysis. The book is well written and interesting but it gives evidence of superior novel writing ability and only questionable evidence of a knowledge of psychotherapeutic procedure. In brief, the plot, supposedly based on a real story from the diary of the man who was being analyzed, tells of a shy and stammering engineer who fell in love, developed an affair and then when his analysis was about over, rejected his mistress and found another woman to whom his marriage is implied at the end of the book. The mistress was fortunate, for the patient became very prosy and dull.

The volume starts out well from the standpoint of demonstrating analytic procedure with a letter from the patient and an office interview which includes a good interpretation of a dream. Other psychoanalytical material appears from time to time in the volume which is somewhat entertaining but contains a great deal of philosophizing about the relations of people to each other according to rather naïve but not unsound psychoanalytical tenets. The value of the book as a means of teaching psychoanalysis is dubious—in fact it is even somewhat misleading; but, as a literary contribution it is superior to many "psychoanalytic novels" and the scattered discussions of psychoanalytic technic are interesting and might be revealing to an interested layman. Apparently for purposes of publication, the sexual picture is softened and this tends to vitiate the analytic picture presented.

L. S. S.

*Handbook of Hematology.* In 4 volumes. Edited by HAL DOWNEY, Professor of Anatomy, Medical School, University of Minnesota, Minneapolis. Thirty-seven contributors. 3136 pages. 1448 illustrations, including 50 colored plates. Paul B. Hoeber, Inc. (Medical Book Department of Harper Brothers), New York. 1938. Price, \$85.00 set. Volume one—pages 1-698.

The publication of this Handbook is significant of the great interest with which the study of hematology is being pursued in all centers of medical research in the United States. This work fills a long existent gap in the English and American literature devoted to hematology. It places at the disposal of all interested in this subject an authoritative, scholarly and critical evaluation of the significant data culled from a world literature of tremendous proportions. The subject is approached from the standpoint of its position as a branch of biological science and hence a large proportion of the entire work, fully one-half, is devoted to a consideration of the fundamental scientific aspects of the field. This necessitates a detailed study of the morphological minutiae of the hematopoietic tissue of both the embryonic and adult human body as well as discussion of comparative hematology. There is of necessity some overlapping of those sections dealing only with a single type of blood cell and those concerned with the origin and interrelationships of these cells. The editor has permitted the contributors a considerable degree of freedom and hence there are divergences of opinion. However, one finds here an equitable expression of all important points of view. The results are both stimulating and thought-provoking to the interested reader. The blood dyscrasias are likewise dealt with in a competent and detailed manner by men who have frequently contributed much original work toward the elucidation of their particular topic.

Volume 1 of the Handbook is concerned almost entirely with a consideration of the fundamental data pertaining to the formed elements of the circulating blood. There are eleven sections, some of which are of monographic proportions. These include chapters on the erythrocytes; the polymorphonuclear neutrophile leukocyte; the eosinophile leukocytes and eosinophilia; the mast cells, including both the tissue and mast leukocyte (basophile); the lymphocytes and monocytes; and the blood platelets and megakaryocytes. There are, in addition, sections on the functions of the leukocytes and three chapters detailing the pros and cons of the supravital method of studying blood cells. The only purely clinical section in this volume is that devoted to a consideration of the hemorrhagic diatheses.

It is obviously impossible within the scope of a brief review to examine critically all the controversial theses discussed. In general it can be stated that the material is presented in such a manner and with such careful documentation that the reader is often stimulated to form his own opinions concerning the data. The existence of so many lacunae in our knowledge of hematology frequently gives a tentative air to many of the discussions. In the section on lymphocytes and monocytes there is a detailed exposition by Bloom of the extreme unitarian theory of blood formation. Included in the same chapter, however, are schemata presenting the other important theories of hematopoiesis. The careful experimental and histological data supporting the monophyletic view of blood cell formation go far toward making this an attractive and rational working thesis. With the introduction of bone marrow biopsy as a clinical diagnostic aid this heretofore academic controversy becomes of vital interest to the clinician. The discussion of hemorrhagic diatheses in volume one illustrates one obvious defect in this type of publication, i.e., its immobility. In dealing with the blood defect in jaundice, for example, there is no mention made of the newer work with vitamin K. The classification of hemorrhagic diatheses does not include the interesting though uncommon "constitutional thrombopathy" of von Willebrand.

The format of the book, its profuse illustrations and extensive bibliographies cannot be commended too highly. It will certainly remain for many years the most authoritative source book for all seeking information in this field and should, moreover, provide a stimulus for further progress in hematology.

M. S. S.

*A Historical Chronology of Tuberculosis.* By RICHARD M. BURKE, M.D. 84 pages; 19.5 × 13 cm. Charles C. Thomas, Springfield, Illinois. 1938. Price, \$1.50.

This small but concise book presents the development of our knowledge of tuberculosis. It is arranged in outline form with the passing years as subheadings to indicate progress.

We find that in general, tuberculosis has developed in the same pattern as the whole field of medicine. The ancient period concerned itself largely with description of the disease. The pre-modern developed the knowledge of anatomy, while the modern period witnessed the development of pathology and bacteriology and finally the climax of our knowledge with Koch's discovery of the tubercle bacillus. Then followed the development of therapy, the rise of anti-tuberculosis activities, and we are brought to the present day concepts.

While of minor value, the book is interesting in that it orients the present with the past and enables one to visualize at a glance the progress of knowledge in this particular field.

M. J.



*Biological and Clinical Chemistry.* By MATTHEW STEEL, Ph.D. 770 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1937. Price, \$8.00.

The author has presented a biochemistry textbook in which attention is pointed toward clinical applications. The book combines theoretical discussions with experiments pertinent to them, often repeating the experiments in different parts of the text. The chapters on vitamins and hormones are especially comprehensive and cover the literature to 1936. References are given at the end of each chapter and suggestions made for further and more complete reading. The book will be useful in laying the foundation for further study and experimentation.

E. M. R.

*Fundamentals of Experimental Pharmacology.* By TORALD H. SOLLMAN, M.D., Sc.D., and PAUL J. HANZLIK, A.M., M.D. 307 pages; 23.5 × 16 cm. J. W. Stacey, Inc., San Francisco. 1939. Price, \$4.25.

Ten years have elapsed since the first publication of this book on experimental pharmacology and those concerned with the teaching of this subject to medical students from an experimental view point welcome the revision of this standard text in the field. The second edition continues the original plan of the first by dividing the text into two general parts: first, Chemical Pharmacology, and second, Experimental Pharmacodynamics. The aim of the author is to provide the fundamentals of Pharmacology for medical science, public health, industry, government agencies and train the students for the fulfillment of these responsibilities by means of a rounded out, practical course of exercises using well-tested methods. Among the subjects treated by the book are, pharmaceutical preparations, incompatibilities, toxicology, adsorption of drugs, osmotic and colloidal phenomena, protoplasmic poisons and anthelmintics. Under experimental pharmacodynamics the action of drugs on the various systems of the body are treated under: central nervous system, cardiac muscle, respiratory reactions, circulatory correlations and changes in urine flow.

The appendices to the book are of special interest containing lists of the equipment necessary for the experiment and the extraordinary useful table of the doses of drugs for various animals required to produce definite effects.

The pharmacologist welcomes the revision of this standard book for experimental work in this ever broadening field.

J. C. K., JR.

## COLLEGE NEWS NOTES

### FIFTIETH ANNIVERSARY OF THE JOHNS HOPKINS HOSPITAL

The fiftieth anniversary of the opening of the Johns Hopkins Hospital was the occasion of a three day celebration attended by a large gathering of the alumni of this institution as well as by many distinguished guests. In one of the opening sessions the greetings of the American Medical Association, of the American Nurses Association, of the American Hospital Association, of the American College of Surgeons and of the American College of Physicians were conveyed in brief addresses by their respective Presidents. These were followed by the principal address of the occasion which was delivered by Dr. James B. Herrick, F.A.C.P. The speech of greeting by the President of the College, Dr. O. H. Perry Pepper, follows:

#### GREETINGS TO THE JOHNS HOPKINS HOSPITAL ON THE OCCASION OF ITS FIFTIETH ANNIVERSARY CELEBRATION, MAY 4, 1939

By O. H. PERRY PEPPER, M.D., President of the American College of Physicians

The American College of Physicians is deeply appreciative of the opportunity to join in this well-justified celebration of the Fiftieth Anniversary of the opening of the Johns Hopkins Hospital.

Its founder, Johns Hopkins, was a member of the Society of Friends and in their phraseology believed that he would "be given to see" how to dispose of his wealth. Would that today he might be "given to see" the wonderful results of his wise bequests! For the foundation of the Johns Hopkins Hospital initiated one of those major advances by which medicine progresses; sometimes it is a discovery such as those of Pasteur or Koch, sometimes a new method, sometimes a new vision stimulating others to convert the vision into reality.

From the opening of the new Hospital untrammelled by tradition, there came new life into medicine as a whole and especially into the teaching and science of medicine, for this was the beginning of real clinical teaching in this country and of the merging of student, interne, resident and staff into one coördinated team for the study of patient and disease.

Let others recall for us the whole brilliant roster of the staff and administration from 1889 to the present. As internists, the Fellows of the American College of Physicians derive their special inspiration not only from this hospital's great first Physician-in-Chief—William Osler, but also from his eminent successors—Barker, Janeway, Thayer and Longcope. Five names to conjure with; five individuals but one unbroken stream of influence; a constant spring from which there have flowed scientific advances and an endless group of internists trained in the Hopkins tradition.

Internal medicine owes much to these five Physicians-in-Chief. The field of internal medicine would not be what it is today if Osler's Textbook and Osler's System of Modern Medicine had not been written; if Barker had not clarified the technic of modern diagnosis in his system, Monographic Medicine. Janeway set us a new standard in giving up the rewards of an almost limitless practice to initiate the full-time experiment; Thayer the many-sided, a leader in medicine, in medical science, in the army and in all medical societies and associations; and Longcope who has carried on the tradition: a teacher, clinician, investigator and author.

And internal medicine has learned much from the scientific studies made on the medical wards of this hospital. It was from here came the classical papers on the visceral manifestations of the erythema group and on polycythemia; the description of the eosinophilia of trichiniasis; the famous monograph on bacterial endocarditis and the more recent studies on the streptococcus and on nephritis, to name only a few.

President Gilman is often credited with having had uncanny skill in selecting that famous first faculty, but it seems that later choices have been just as happy. The American College of Physicians would have been proud to have counted all of these men among its members but it was not founded in time. It has, however, included in its Fellowship not only Dr. Thayer, Dr. Barker and your present Physician-in-Chief, but many of the graduates of this Hospital.

That so many different aspects of Medicine are represented here today is significant of the solidarity of medicine as a whole and of the interdependence of its various divisions. The hospital, the doctor, the nurse, and all those agencies directed to scientific progress and medical education, graduate and undergraduate, together form that whole we call Medicine.

And it is to Medicine in this all inclusive sense that we have each devoted our lives. Some are enlisted in one branch of the service, some in another; some are grouped for one purpose, others for another, but all have joined for the duration of an endless war, striving to reach an unattainable goal. Individually and collectively we love and serve that discipline, system, craft or art called Medicine. To advance Medicine we must give ourselves unselfishly, and we must integrate our organized efforts to this end.

Today we are celebrating not the mere existence of the Johns Hopkins Hospital for the period of fifty years but the remarkable influence of this institution on Medicine during the past half century. This has been an era of amazing medical progress and to this the Johns Hopkins Hospital has greatly contributed and is contributing today.

It is very proper, therefore, that both as individuals and as representatives of groups dedicated to this same end we should congratulate the Johns Hopkins Hospital upon its past achievement, its present vitality and its promise for an even brighter future. In the name of the American College of Physicians it is my privilege to deliver this greeting to the Johns Hopkins Hospital on its fiftieth anniversary.

#### THE NEW ORLEANS SESSION

The Twenty-Third Annual Session of the American College of Physicians, held in New Orleans, was an eminently successful one. All meetings were well attended, including those of the executive boards.

On the evening preceding the opening of the Session, there was a combined dinner of the Board of Regents and the Board of Governors, with members of the Committee on Postgraduate Education, members of the American Board of Internal Medicine, local committee men from New Orleans and the Secretary of the Council on Medical Education and Hospitals of the American Medical Association present. The meeting was devoted to a discussion of graduate and postgraduate medical education, including not only the intensive postgraduate courses which are now being sponsored by the College, but also a discussion of the training and facilities for specialization in internal medicine or one of the allied specialties. The meeting was attended by 22 Officers and Regents, 45 Governors and 15 guests, and the majority of those present engaged in the discussion. At this meeting there was a report on the registration and attendance at the post-graduate courses sponsored by the College during the two-week period just preceding the New Orleans Session, which report herewith follows:

	General Medicine Baltimore	Cardiovascular and Respira- tory Diseases Baltimore	Cardio-Renal- Vascular Medicine Chicago	Cardio- vascular Diseases St. Louis	Diseases of the Glands of In- ternal Secre- tion St. Louis	Total
ALABAMA.....					2	2
CALIFORNIA.....			1			1
COLORADO.....			1			1
CONNECTICUT.....	3					3
DISTRICT OF COLUMBIA.....	5					5
FLORIDA.....	2					2
GEORGIA.....	4					4
IDAHO.....			1			1
ILLINOIS.....		1	1		1	3
IOWA.....				1		1
KANSAS.....					4	4
KENTUCKY.....			1	1	1	3
LOUISIANA.....		1				1
MAINE.....	1					1
MARYLAND.....	2	3				5
MASSACHUSETTS.....	4		1	1		6
MICHIGAN.....	2	1	4	1		8
MISSOURI.....	1					1
MONTANA.....					1	1
NEBRASKA.....	1		1	2		4
NEW JERSEY.....		1				1
NEW YORK.....	7	1	2		1	11
NORTH CAROLINA....	2		1			3
OHIO.....	2	1	1	1	2	7
OKLAHOMA.....				1	1	2
OREGON.....			1			1
PENNSYLVANIA.....	8	4	2	1		15
TENNESSEE.....	1				1	2
TEXAS.....	1					1
VERMONT.....	1					3
VIRGINIA.....	1	1		1		3
WASHINGTON.....			2	1	1	4
WEST VIRGINIA.....	1			1	1	3
WISCONSIN.....	1		2	1		4
HAWAII.....			1			1
CANADA:						
New Brunswick..		1				1
Ontario.....	1					1
	51	15	23	13	16	118

An analysis of the registration at the New Orleans Session discloses the largest gross registration in the history of the College, 2675; but the net physician attendance ranked in fourth place. There were 578 ladies registered, a number greatly exceeding that of any previous meeting. A comparison of the registration for the past five years follows:

	Mem- bers	Guest Physi- cians	Guest Non- Physi- cians	Stu- dents	Ex- hibi- tors	Ladies	Misc.	Total
New Orleans (1939)	891	524	10	499	167	578	6	2675
New York (1938)	1447	463	24	3	291	319		2547
St. Louis (1937)	877	589	30	414	201	210		2321
Detroit (1936)	733	539		172	132	103		1679
Philadelphia (1935)	923	749		346	231	195		2444

At the New Orleans Session the attendance records show that there were physicians present from forty-seven States of the United States, five Provinces of Canada, the Canal Zone, Hawaii, Puerto Rico, China and Mexico.

The full personnel of new committees, Officers, Regents and Governors appear on the inside cover pages of this issue (May).

At the conclusion of the Session there was a post-convention tour to Mexico City, patronized by a group of twenty-seven, consisting of members of the College and their families. Still a larger group of approximately eighty physicians and their families returned to New York on a post-convention cruise by way of the S. S. Dixie. Both post-convention trips were highly successful and contributed much to the enjoyment and pleasure of those participating.

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#### 1940 SESSION OF THE COLLEGE

Dr. Howard T. Karsner, F.A.C.P., of Western Reserve University School of Medicine, has been appointed General Chairman of the Twenty-Fourth Annual Session of the College, to be held in Cleveland, Ohio, April 1-5, inclusive, 1940.

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#### *Correction*

In the obituary of the late Dr. Carl Boettiger, appearing in the March, 1939, issue of the ANNALS OF INTERNAL MEDICINE, it should have been stated that during the World War Dr. Boettiger was in charge of the Laboratory of the Base Hospital at Camp Bowie, instead of in charge of the Base Hospital.

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#### CENTENNIAL CELEBRATION OF DUKE UNIVERSITY

Upon appointment by ex-President Kerr, Dr. Charles H. Cocke, Governor of the State of North Carolina, was the official delegate of the American College of Physicians to the centennial celebration of Duke University at Durham, April 21-23. The academic procession was notable for its size, there being present approximately 90 per cent of the representatives of the 395 universities, colleges, scientific and literary organizations which had accepted. Addresses were delivered by Dr. John H. Finley, President H. M. Wriston, Dr. Eduard Benes, late President of Czechoslovakia, and by President Dodds of Princeton.

Through the courtesy of its official delegate, the American College of Physicians was presented with a bound autographed copy of "The Architecture of Duke University."

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#### NEW LIFE MEMBER

Dr. Alexander G. Brown, Jr., F.A.C.P., Richmond, Va., became a Life Member of the American College of Physicians on April 10, 1939.

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#### GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

#### *Reprints*

Dr. Thomas W. Baker (Associate), Charlotte, N. C.—7 reprints;  
Dr. Edward G. Billings (Associate), Denver, Colo.—2 reprints;  
Dr. Preston V. Dilts (Associate), Pittsfield, Ill.—1 reprint;

Dr. Alfred Winfield Dubbs (Associate), Allentown, Pa.—1 reprint;  
 Dr. Edgar Durbin, F.A.C.P., Denver, Colo.—1 reprint;  
 Dr. Norbert Enzer, F. A. C. P., Milwaukee, Wis.—1 reprint;  
 Dr. James William Finch (Associate), Hobart, Okla.—1 reprint;  
 Dr. A. Allen Goldbloom, F.A.C.P., New York, N. Y.—1 reprint;  
 Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—6th Supplement, Second Series, to  
 "Modern Drug Encyclopedia";  
 Dr. Howard T. Karsner, F.A.C.P., Cleveland, Ohio—19 reprints;  
 Dr. Samuel R. Kaufman (Associate), Wilkes-Barre, Pa.—1 reprint;  
 Dr. William H. Kraemer, F.A.C.P., Wilmington, Del.—1 report;  
 Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, Pa.—5 reprints;  
 Dr. Arthur J. Logie (Associate), Jacksonville, Fla.—2 reprints;  
 Dr. Thomas H. McGavack, F.A.C.P., New York, N. Y.—2 reprints;  
 Dr. Frank B. Queen (Associate), Chicago, Ill.—1 reprint;  
 Dr. Louis H. Sigler (Associate), Brooklyn, N. Y.—1 reprint;  
 Dr. H. A. Slesinger (Associate), Windber, Pa.—1 reprint;  
 Dr. William H. Walsh, F.A.C.P., Chicago, Ill.—2 reprints;  
 Dr. Burton L. Zohman, F.A.C.P., Brooklyn, N. Y.—1 reprint.

Acknowledgment is also made to Dr. J. R. Schramm, Professor of Botany at the University of Pennsylvania, of his gift of a reprint entitled "Cost Analysis of Scholarly Periodical Printing," from the Proceedings of the American Philosophical Society.

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Dr. Edward Bigg (Associate) has accepted an appointment as Instructor in the Department of Medicine of the University of Chicago, beginning July 1, 1939. Dr. Bigg has held a similar position in the Department of Medicine of the University of Michigan.

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Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, has been promoted to Assistant Professor of Medicine in charge of the Department of Cardiology at the Woman's Medical College of Pennsylvania.

Dr. Leaman addressed the West Philadelphia Medical Association January 24, 1939, on "Some Curable Types of Heart Disease"; the Montgomery County Medical Society March 1 on "Prognosis in Heart Disease"; the New Castle County Medical Society at Wilmington, Del., March 21, on "Heart Block and the Adams-Stokes Syndrome"; the Atlantic County Medical Society, April 14, on "Modern Trends in the Treatment of Cardiovascular Disease"; the American Association of the History of Medicine at its fifteenth annual meeting, Atlantic City, May 1, on "Medical History in Clinical Teaching."

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Dr. L. Minor Blackford, F.A.C.P., Atlanta, Ga., was recently promoted from Instructor to Associate in Medicine at Emory University School of Medicine, Associate Visiting Physician at Emory University Hospital and Assistant Physician in the Emory University Division of Grady Hospital.

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Recent announcement was made by President Winfred G. Leutner of Western Reserve University, Cleveland, of a grant of \$4,100 to Dr. Carl J. Wiggers, F.A.C.P., Professor of Physiology of the School of Medicine, from the John and Mary Markel Foundation, of which J. Pierpont Morgan is President, whose object is "to support research programs in medical science." This grant is for a study of the nature of ventricular fibrillation by means of desensitizing the heart.

Dr. Edward Strecker, F.A.C.P., Philadelphia, delivered a Salmon Lecture before the New York Academy of Medicine on April 14, 21 and 28, and before the University of Toronto on May 5, his subject being "Beyond the Clinical Frontiers." Salmon established a fund of \$100,000 in the field of psychiatry and the lectureship has been assigned for approximately seven years. The lecturer receives the income from the fund, amounting to about \$2,500. He must deliver a series of lectures and present the manuscript for a book.

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Dr. Frank S. Horvath, F.A.C.P., Washington, D. C., was appointed Medical Director of the Outpatient Department of Georgetown University Hospital and Director of Student Instruction in the same department on March 1.

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Dr. Samuel M. Feinberg, F.A.C.P., Chicago, addressed the Michigan Allergy Society at Ann Arbor on March 16 on "Mold Allergy." He also addressed the Boone-Story County (Iowa) Medical Society on March 22 on "The Rôle of the General Practitioner in Allergy."

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Dr. H. I. Spector, F.A.C.P., St. Louis, was the guest of the Sedgwick County Medical Society, Wichita, Kan., at their Third Spring Clinical Assembly on March 21, 1939. In the morning he spoke on the subject of "Treatment of Pulmonary Tuberculosis with Special Emphasis on Collapse Therapy." At the noon meeting he conducted a round-table discussion and in the evening he spoke on the subject of "Differential Diagnosis of Hemoptysis."

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Under the presidency of Dr. Samuel E. Munson, F.A.C.P., College Governor for Southern Illinois, the Illinois State Medical Society held its 99th annual meeting at Rockford, Ill., May 2, 3, and 4, 1939. Dr. Munson's presidential address was entitled, "Shall Organized and Scientific Medicine Continue Its Progress."

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The Alameda County Tuberculosis and Health Association conducted a panel discussion and demonstration of tuberculosis prevention and treatment at Oakland, Calif., on April 19. Among those appearing on the panel were Dr. B. W. Black, F.A.C.P., Medical Director of Alameda County; Dr. Harold G. Trimble, F.A.C.P., Chief of the Tuberculosis Service, Alameda County Institutions; and Dr. Chesley Bush, F.A.C.P., Superintendent of Arroyo Del Valle. The panel discussion included the presentation of patients, methods and technics of treatment and prevention.

## RECENT ANNOUNCEMENTS

The University of Wisconsin Medical School is to conduct an Institute for the Consideration of the Blood and Blood-Forming Organs, September 4-6, 1939. The program is to include papers and round-table discussions by European and American workers in the field of hematology. In addition to the discussions, the following formal papers are to be presented:

- Dr. L. J. Witts, Oxford, England, Anemias Due to Iron Deficiency.
- Dr. Cecil J. Watson, Minneapolis, The Porphyrins and Diseases of the Blood.
- Dr. Cornelius P. Rhoads, New York, Aplastic Anemia.
- Dr. E. Meulengracht, Copenhagen, Denmark, Some Etiological Factors in Pernicious Anemia and Related Macrocytic Anemias.
- Dr. Harry Eagle, Baltimore, The Coagulation of Blood.
- Dr. George R. Minot, Boston, Anemias of Nutritional Deficiency.
- Dr. Russell L. Haden, Cleveland, The Nature of the Hemolytic Anemias.
- Dr. Jacob Furth, New York, Experimental Leukemia.
- Dr. Claude E. Forkner, New York, Monocytic Leukemia and Aleukocythemic Leukemia.
- Dr. Edward B. Krumbhaar, Philadelphia, Hodgkin's Disease.
- Dr. Louis K. Diamond, Boston, The Erythroblastic Anemias.
- Dr. Edwin E. Osgood, Portland, Marrow Cultures.
- Dr. Charles H. Doan, Columbus, The Reticulo-Endothelial System.
- Prof. Hal Downey, Minneapolis, Infectious Mononucleosis.
- Dr. Paul Reznikoff, New York, Polycythemia.

Physicians and others who are interested are cordially invited. A detailed program may be obtained by addressing Dr. Ovid O. Meyer, Chairman of Program Committee, University of Wisconsin Medical School, Madison, Wisconsin.

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The Twelfth Graduate Fortnight of The New York Academy of Medicine will be held from October 23 to November 3, 1939.

The subject of this year's Fortnight is THE ENDOCRINE GLANDS AND THEIR DISORDERS.

The Fortnight will present a carefully integrated program which will include clinics and clinical demonstrations at many of the hospitals of New York City, evening addresses, and appropriate exhibits. The evening sessions at the Academy will be addressed by recognized authorities in their special fields, drawn from leading medical centers of the United States. The comprehensive exhibit will include books and roentgenographs; pathological and research material; and clinical and laboratory diagnostic and therapeutic methods. It is also planned to provide demonstrations of exhibits. All members of the medical profession are eligible for registration.

A complete program and registration blank may be secured by addressing Dr. Mahlon Ashford, The New York Academy of Medicine, 2 East 103 Street, New York City.

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Vanderbilt University Medical School has announced a graduate course in Internal Medicine designed for those desiring special training in this field.

The course will extend over a period of one year and will be open to physicians who have completed an internship, have had an additional year's experience as assistant resident in medicine or its equivalent and are acceptable to the school. The first course will begin July 1, 1939, and is limited to six students. Tuition fee—\$300.



Three fellowships are available for the course. These fellowships, which provide tuition, board, and lodging, are open to those who meet the requirements mentioned above and will be awarded on the basis of the individual's training and recommendations.

Applications for the course and the fellowships will be received by the Director of Postgraduate Instruction, Vanderbilt University Medical School, from whom further information regarding the course and the fellowships can be obtained.

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The cardiovascular department of the Michael Reese Hospital (29th and Ellis Ave., Chicago, Illinois) offers a full-time intensive course in Electrocardiography (August 21-September 2, 1939) by Dr. Louis N. Katz, Director of Cardiovascular Research.

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The Fourth Annual Convention of the National Gastroenterological Association will be held on June 1 and 2, 1939, at Squibb Hall, Squibb Building, 745 Fifth Avenue, New York, N. Y. A very interesting program is assured.

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The American Congress on Obstetrics and Gynecology, which will meet in Cleveland (September 11-15, 1939), has a section on Medicine and a section on Public Health. The preliminary programs of these two sections have been issued and contain many papers which are of interest to all internists. Registration fee to the Congress will be \$5.00. Applications may be addressed to The American Congress on Obstetrics and Gynecology, The Annex, 650 Rush Street, Chicago, Illinois.

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The Society for Investigative Dermatology and the Journal of Investigative Dermatology were recently inaugurated. This Society and its Journal are serving to bring together scientific investigators who are particularly interested in studies in dermatology and venereology and in using the skin as a test tissue for the study of fundamental problems. Membership is open to any physician in good standing or one engaged in teaching or in scientific research in medicine or allied subjects in a reputable university, college, laboratory, hospital or other institution. The secretary is Dr. S. W. Becker, School of Medicine, University of Chicago, Chicago, Illinois.

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Announcement has been made of a new scientific periodical entitled "Psychosomatic Medicine" to be published quarterly (January, April, July and October) with the sponsorship of The Committee on Problems of Neurotic Behavior, Division of Anthropology and Psychology—National Research Council. Each number is to consist of approximately 125 pages totaling between 500 and 600 pages per volume. An Editorial Board, all specialists in their fields, has been organized to reach prompt decision upon all contributions submitted.

The aim of Psychosomatic Medicine is to encourage and bring together studies which make a contribution to the understanding of the organism as a whole, in somatic and psychic aspects. These materials are now usually separated widely in manner and place of publication because of differences in concept, approach and methods. The sponsoring groups feel that this constitutes an urgent practical need for a new channel of scientific interchange. This journal will provide both an integrating medium and a means of prompt and inexpensive publication.

Subscriptions to Psychosomatic Medicine for one year will be \$5.00; for two years, \$9.00 (outside U. S. and Canada: for one year, \$5.50; for two years, \$10.00); single copies, \$1.75. They should be addressed to Dr. Flanders Dunbar, Managing Editor, 2 East 103rd Street, Room 445, New York, N. Y.

For the past three years the RADIOLOGIC REVIEW AND MISSISSIPPI VALLEY MEDICAL JOURNAL has served as the official publication of the Mississippi Valley Medical Society and has devoted most of its pages to this purpose. With the continued growth of that society it has seemed fitting that the name of its official publication more clearly indicate its principal function, hence the new name—"MISSISSIPPI VALLEY MEDICAL JOURNAL (Incorporating the RADIOLOGIC REVIEW)." Like its predecessor, the new publication will be a bimonthly and essentially clinical, especially appealing to the general practitioner. Subscriptions should be addressed to Dr. Harold Swanberg, Editor, Mississippi Valley Medical Journal, P. O. Drawer 110, Quincy, Illinois.

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The Medical Faculty of the University of Paris, in collaboration with the Association pour le Développement des Relations Médicales and the American Medical Society of Paris, has organized courses in English for graduates in medicine. The cost of a course is generally six dollars per lesson, whether taken privately or by a group, and is divided between the students.

The Faculty of Medicine will grant, for post-graduate work done here, a certificate, to physicians who are graduates of a reputable medical college and who have taken courses during a period of no less than two months in Paris. Those certificates will bear the Dean's signature.

For all inquiries, apply to the office of the Association pour le Développement des Relations Médicales (A.D.R.M.), Salle Bécлар, Faculté de Médecine, 12, rue de l'Ecole-de-Médecine, Paris.

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The Istituto Di Malariologia at Rome offers international courses in malariology this year from July 25 to September 20. These courses will include instruction in the laboratory aspects of malarial disease, in the pathology and clinical aspects of malaria, in malarial entomology, epidemiology and prophylaxis. In addition to lectures and demonstrations there will be practical work in the laboratory and wards, residence in experimental stations, and excursions to malarial regions in Italy.

The course is open exclusively to postgraduate physicians. It is stated that it will be held in French if required and if 10 students are attending. In any case, one or more interpreters will be available. Tuition fee, including obligatory trips, is 400 Lire. Applications must be received before June 20, 1939, and should be addressed to The Director, G. Bastianelli, Istituto Di Malariologia "Ettore Marchiafava," Rome, Italy.

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The German authorities for postgraduate medical instruction have arranged a number of international courses for specialists for the summer of 1939.

All courses will be held in the German language. The number of participants is limited.

Information and prospectuses through:

Ärztliches Fortbildungswesen, Berlin N. W. 7., Robert-Kochplatz 7, Kaiserin-Friedrich-Haus.

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The Seventh Congress of Biologic Chemistry will meet in Liège, Belgium, from October 13-15, 1939.

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The National Library of Peiping (Kunming, China) states that, in order to keep Chinese scholars informed as to the recent development of various branches of science, the Library is building up a special Reprint Collection which will be of great value to investigators engaged in scientific research. They are in urgent need of books and periodicals of all kinds, old or new, especially standard works in various fields. Donations of reprints and books from American and Canadian authors may be sent care of the International Exchange Service, Smithsonian Institute, Washington, D. C., which makes monthly shipment to China.



DR. ALFRED STENGEL  
MASTER OF THE AMERICAN COLLEGE OF PHYSICIANS

*OBITUARIES*

## DR. ALFRED STENGEL

## AN APPRECIATION

There are some who possess that intangible quality known as leadership, to whom all others turn for counsel, guidance and inspiration. Such a man was Alfred Stengel whose sudden and unexpected death on April 10, 1939 deprived American Medicine of one of its most distinguished clinicians and robbed the American College of Physicians of a beloved and honored Master as well as a loyal and ardent champion.

Dr. Stengel was born in Pittsburgh, Pa. on November 3, 1868. He received his medical degree from the University of Pennsylvania in 1889, after attending the Biological Department of the University of Pennsylvania. In the early part of his career he devoted himself enthusiastically to pathology, thereby laying a firm foundation for the years of achievement in clinical medicine that were to follow. He not only served as Pathologist to the Lankenau Hospital and as one of the pathologists at the Philadelphia General Hospital, but also published a justly popular and widely used Text-book of Pathology. His career as a clinical teacher began with his appointment as Instructor in Clinical Medicine at his Alma Mater in 1893. By the age of 30, he was made Clinical Professor of Medicine, a post which he held until he became Professor of Medicine at the University of Pennsylvania in 1911. It was during these years that he gained his well deserved popularity with students and physicians alike as an astute clinician and a scholarly, brilliant teacher whose clinical lectures were masterpieces of concise expression and clear thinking. From the time of his appointment, until his retirement as Professor of Medicine in 1936, he showed a keen interest in and a profound understanding of the problems of medical education, re-organizing the Department of Medicine at the University of Pennsylvania and introducing many far reaching and important changes. As a result of his versatility and ability, he was the first appointee as Vice President in Charge of Medical Affairs of the University of Pennsylvania. With characteristic unselfishness, he assumed this difficult position in 1931. In this post he had unusual opportunities to demonstrate his exceptional ability as an administrator. Dr. Stengel accomplished the arduous and important task of coördinating all the various medical activities and allied departments of the University of Pennsylvania and the present efficient organization is a tribute to his foresight and genius.

During his years of active medical practice and teaching, he served as Physician to a number of the leading hospitals of Philadelphia, including the Pennsylvania Hospital, the Hospital of the University of Pennsylvania and the Philadelphia General Hospital. In recognition of his great contributions to medical science and to medical education in this country, he was accorded the honorary degrees of LL.D. from the University of Pennsylvania, Sc.D. from the University of Pittsburgh and LL.D. from Lafayette College.

Not long after his graduation, he became associated with that outstanding figure in American Medicine, the late Provost of the University of Pennsylvania, Dr. William Pepper, who early recognized in the young Alfred Stengel, a man destined to take a conspicuous place in the medical activities, not only of Philadelphia, but of the nation. This close association with the brilliant Pepper had a profound effect upon the development of the alert, energetic and keen minded Stengel.

Dr. Stengel made numerous outstanding contributions to the leading medical works of his time, among the most important of which were: Diseases of the Blood to Twentieth Century Practice, Diseases of the Intestines in Osler's Modern Medicine, Diseases of the Liver in Nelson's Loose Leaf System of Medicine, in addition to many others of equal importance. For a number of years he edited the American Journal of Medical Sciences. One of the literary achievements of which he was most proud was his editorship of the English edition of Nothnagel's System of Medicine.

The eagerness with which Dr. Stengel's advice was sought by various groups is well illustrated by his membership on the following boards: Board of Managers of the University Hospital, of the Wistar Institute of Anatomy, of which Board he later became President, of the Graduate Hospital of the University of Pennsylvania and the Pepper Clinical Laboratory of which he became the Director, as well as the Board of Trustees of the University of Pennsylvania. In these capacities, he was able to exercise a far reaching influence in the conduct of the affairs of the University of Pennsylvania. He was a member of many important national medical societies including the Association of American Physicians and that venerable organization, The American Philosophical Society. One of the greatest honors that came to him was that of being President for three successive terms of that august body, The College of Physicians of Philadelphia.

His activities and accomplishments in the field of medicine and the medical sciences, as well as his influence upon the City of Philadelphia and his Alma Mater, might be dwelt upon at great length, but the interest of the American College of Physicians in Dr. Stengel is not based primarily upon the fact that he was an outstanding clinician, a brilliant teacher and an able administrator, but rather upon his never failing interest in and contributions to our organization.

In 1923 he became a Fellow of this College. About this time, it became apparent that, if the College was to attain the high purposes for which it was organized, changes must be brought about in its administration. To Dr. Stengel, it was obvious that a critical point in the history of the College had been reached. With characteristic energy and wisdom, he applied himself to the task of saving the College by bringing about a much needed reorganization. The eminent position and the influence which the College exercises today in American Medicine are largely the result of Dr. Stengel's foresight and determination. It is not surprising, therefore, that in 1925 he became

the Fourth President of the College and, in spite of the great press of other work, consented to serve as President a second term in order to complete the extensive changes that he had instigated. In 1926 he became the first Life Member of the College. In recognition of his outstanding service to the College and his preëminent position in medicine, he became its Second Master in 1929. From the time that he retired from the Præsidency to the day of his death, Dr. Stengel served continuously on the Board of Regents or on some committee of the College. In 1935 he was the General Chairman of the Annual Clinical Session that was held in Philadelphia. From the time when he first became a Fellow, Dr. Stengel evinced untiring interest in the affairs of the American College of Physicians. It may be said, without fear of contradiction, that he laid the foundation for the high academic standards and sound economic policies that are today characteristic of the College and, through his example and inspiration, he did much to bring the College to the point where it exercises an important national influence in Internal Medicine.

Dr. Stengel's loss will be keenly felt throughout the College but especially by those who have had the privilege of being closely associated with him during his years of activity in this organization.

GEORGE MORRIS PIERSOL, M.D., F.A.C.P.,  
Secretary General, American College of Physicians.

### DR. AMOS HENRY STEVENS

Dr. Amos Henry Stevens, prominent Fairmont, West Virginia, internist, and for ten years Secretary of the Marion County Medical Society, died suddenly at his home on March 11, 1939, following a heart attack. He was 40 years of age.

Dr. Stevens was born in Portland, Maine, on July 23, 1899. Following his early education there, he attended the Massachusetts Institute of Technology, graduating in 1922. He received a Certificate of Public Health from the same institution in 1923. In 1926 he received his M.D. degree from Harvard University. Then followed two years internship at the Henry Ford Hospital.

Dr. Stevens located in Fairmont early in 1929 and served for one year as Chief of the Fairmont City Hospital Medical Staff. The same year he was elected Secretary of the Marion County Medical Society, a position he held until shortly before his death. In addition to his many other medical organization activities, he was a member of the Syphilis Committee of the West Virginia State Medical Association and was particularly interested in syphilis control work.

Dr. Stevens, as well as being affiliated with county, state, and national associations, was a Fellow of the American College of Physicians, a Diplomate of the American Board of Internal Medicine, and a 1927 Diplomate

of the National Board of Medical Examiners. His practice was limited to internal medicine and he was recognized by his associates as one of the outstanding internists of Northern West Virginia.

Funeral services were held on March 14, and interment was made in the family burial ground, Arlington, Massachusetts. Dr. Stevens is survived by his wife, Julia Stevens, former President of the Womans Auxiliary to the State Association, and three sons.

ALBERT H. HOGE, M.D., F.A.C.P.

Governor for West Virginia.

# ANNALS OF INTERNAL MEDICINE

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## LOCAL INJECTIONS AND REGIONAL ANALGESIA WITH PROCAINE SOLUTIONS FOR INTRACT- ABLE PAIN IN CHRONIC ARTHRITIS AND RELATED CONDITIONS \*

By OTTO STEINBROCKER, M.D., F.I.C.A., *New York, N. Y.*

### INTRODUCTION

ARTHRITIS and related diseases present systemic and local symptoms not infrequently dominated chiefly by persistent, intractable pain or discomfort. Certain of these rheumatic conditions are preëminently painful, such as neuritis, bursitis, fibrositis and traumatic conditions of muscle, tendon, fascia and joint. While rheumatoid arthritis often is associated with discomfort, it is not as likely to present localized, intractable involvement of one or more joints, as osteoarthritis. We have been impressed by the frequency of severe, localized pain in many of these ailments, for which ordinary systemic and local measures fail to give sufficient or enduring relief.

In rheumatic disease especially, the tendency towards chronicity is aggravated by the accompanying pain. A vicious cycle of pain, muscle spasm, postural defect, disability and deformity often arises. A good part of this picture is functional and depends largely upon the underlying painful state. The appearance of advanced arthritis and related disease frequently suggests that this secondary functional cycle, although starting as a by-product of the disease, becomes responsible for many of the terminal organic changes and trophic disturbances. Because of the dynamic rôle played by localized pain in these conditions, we have sought some means of more satisfactory control of articular and allied discomfort until the usual measures achieve their more gradual effects.

The effort to relieve the arthritic by palliative, local remedies was embodied in the most primitive, as well as modern, concepts of arthritis. Treat-

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\* Received for publication June 15, 1938.

From the Arthritis Clinics, Bellevue Hospital, Fourth Medical Division, and N. Y. Post-Graduate Hospital and Medical School (Columbia University).



ments such as liniments, packs, hydrotherapy and physiotherapy in all its forms, are time-worn remedies based on this universally accepted principle. Although possessing definite value in ordinary situations these established measures at times prove inadequate for severe or intractable complaints. In considering this subject several years ago, we felt that local injections at the site of pain or irritability, at the point of pain radiation, or, finally, at the source of nerve supply to the involved part might be a helpful and logical procedure. Such an approach is not entirely new. Among others, the late J. B. Murphy<sup>1</sup> of Chicago, a number of years ago, injected a 2 per cent solution of formalin in glycerine into arthritic joints, particularly when effusion was present. Charles H. Mayo<sup>1</sup> used a 5 per cent solution of iodoform in olive oil for injection of the osteoarthritic hip. Some 30 years ago, Morris<sup>2</sup> devised a special preparation for injection into affected knees. In Europe various fatty preparations are being introduced into osteoarthritic joints.<sup>3</sup>

Comprehensive, interesting work in this direction has been published by Forestier,<sup>4</sup> who employed lipiodol for periarthritic, perineural, periosseous, paravertebral, and intrarticular injections. He has reported satisfactory relief of pain by this method, notably in osteoarthritis and the various neuritides. A variety<sup>5</sup> of other substances have been used and advocated in this form of local and regional injection therapy,—urea and quinine solution, hypertonic dextrose solution, salines, methylthionine chloride, camphor, antipyrine, sulfur, iodine, pitcher plant extract, formic acid, alcohol, and a host of complex anesthetic formulae with some of which we have had limited or unsatisfactory experience. Deep roentgen-ray therapy<sup>5</sup> has given variable results.

As a result of our investigation of a number of preparations at the beginning of this work, we decided to limit our observations to procaine solution, 1 to 2 per cent, because of the reliable and consistent, though brief, response we obtained with practically no adverse effects. It is pertinent to add here that similar, favorable results have been reported abroad in the use of aqueous procaine solution, most extensively by Leriche and his co-workers,<sup>6</sup> de Sèze,<sup>6</sup> and others<sup>6</sup> in traumatic arthritis and in many traumatic, rheumatoid and degenerative, skeletal conditions.

As we proceeded, however, it became apparent that a substance with more prolonged action than aqueous procaine solution was desirable in some cases. We, therefore, instituted the study of 2 per cent procaine base in oil. We found this oily preparation an improvement over the aqueous in some procedures and have continued its use. The value of an oily medium in slowing absorption of the anesthetic agent and in that way prolonging analgesia has been described,<sup>7</sup> particularly in rectal surgery,<sup>8</sup> where resort to a variety of oil-soluble anesthetics has become widespread.

## THE EFFECT OF LOCAL INJECTIONS

Our observations have led us to believe that local and regional injection therapy has the advantage of permitting the application of analgesic medication close to, or at, the exact site of pain or irritation, or at the source of nerve supply and pain radiation in arthralgias and related painful states.

We have noted 1 to 2 hours of local anesthesia and from 1 to 3 days of varying degrees of analgesia when aqueous procaine solution has been administered at the proper location with correct technic. The effects of procaine in oil appear to be similar to those of the aqueous solution with greater duration. The oily preparation produces, roughly, at least one and one-half to twice as long a period of analgesia. When the pain returns after treatment, usually with diminished intensity, the site is reinjected and the procedure may have to be repeated at intervals of 3 to 5 days to 2 to 3 weeks, depending upon the severity of the complaint. In severe acute, or chronic, conditions local injection daily may be required for several treatments.

We have injected some patients once and a few 10 to 12 times before lasting relief was accomplished. The aqueous solution may always be employed, but the oil is sometimes contraindicated, as in brachial plexus block. The oily solution in many of the patients produces a local inflammatory, foreign body reaction of varying degree for 1 to 3 days. Occasionally a transient systemic reaction with slight fever may follow.

The sedimentation rate and blood picture appear to be uninfluenced by analgesic therapy.

## METHOD

Procaine solution, aqueous or oily, has been employed by us for several years in selected cases for periarticular, intramuscular, intraligamentary, perineural, intraneural, paravertebral, caudal and a variety of other local injections at the site of pain or at the source of innervation to the painful part. Like others we have found these procedures valuable in a number of acute, painful, skeletal conditions. This report includes, however, only patients with chronic ailments in which treatment by diverse, established measures by ourselves or elsewhere in most cases had failed to give adequate relief.

This study was initiated, and most of the patients were treated, in the Arthritis Clinic of the Fourth Medical Division, Bellevue Hospital; the remainder were injected in the Arthritis Clinic of the N. Y. Post-Graduate Hospital, and in private practice. The present report embraces a variety of pathological sites and, therefore, a number of different technical approaches. The therapy described involves basically the application of accepted regional anesthetic methods to the relief of arthritis and related pain. Wherever possible, we have studied simple, local means of approach offering prospects of general usefulness.

## INDICATIONS FOR ANALGESIC INJECTIONS

The therapeutic procedures under discussion are indicated when, after thorough physical examination and study, visceral disease has been ruled out as the source of pain. In such situations regional and local injections are a valuable adjunct, when the usual measures have failed to provide adequate comfort. In traumatic, rheumatoid, or degenerative processes of joints, periarticular tissues, nerves, bursae and muscles, correct injection therapy offers a promising final resort. As a preliminary measure before employing drastic surgery for intractable pain, repeated regional or local analgesic injection, or finally alcohol block, should be considered in some cases.

## CONTRAINDICATIONS

Regional and local injection therapy with analgesic solutions or alcohol should not be employed if preferable surgical measures, as a result, would be delayed. Uncontrolled diabetics are not suitable subjects. Local injections should not be administered at proposed sites which are infected or located adjacent to an area of infection; in fact, great caution or postponement is advisable when infection is present in any part of an involved extremity. Patients in extremis, or even severely debilitated individuals, should not receive regional or local analgesia if a minor shock is likely to hasten death. Great care must be exercised, and the results carefully evaluated, when injecting extremely apprehensive or neurasthenic individuals in whom a great part of the symptomatology arises from emotional or psychological factors. Psychalgia<sup>10</sup> must first be ruled out in these cases. Patients known to be sensitive to procaine or its derivatives should receive other treatment. A promising substitute recently developed, and effective in our experience so far, is beta-diethylaminoethyl, *p*-ethoxy benzoate hydrochloride, which is reported<sup>2</sup> to have the further advantage of twice the anesthetic duration of procaine hydrochloride.

The local procedures considered here may be followed safely by any practitioner thoroughly familiar with the anatomy and the method detailed, with due regard for the indications, contraindications and precautions already discussed. Paravertebral and brachial plexus block should be employed only by those trained in the technic of regional anesthesia.

## PRECAUTIONS IN GIVING REGIONAL AND LOCAL INJECTIONS

The patient should be in a calm and comfortable position to assure relaxation of the musculature. We employ routine preliminary sedation with phenobarbital, a 1½ grain tablet administered orally 20 to 30 minutes before treatment.

In these injections, as Dutton and Lake<sup>9</sup> emphasize, regurgitation of solution along the needle track is avoided by using the smallest gauge needle

adequate for the occasion, by quick withdrawal of the needle, and by immediate application of pressure over the site, followed by gentle massage for 1 to 2 minutes.

Aspiration always is made before injecting and is repeated intermittently during administration, to be sure the needle has not entered a blood vessel; if blood returns, the needle is withdrawn and gentle pressure used for several minutes. The puncture is repeated then at a short distance from the first point of penetration and the treatment completed in a similar way. An injection given too superficially will be followed by bulging and may alarm the patient unless previous warning has been given.

After-pains for several hours or longer at times may follow injection. They are due usually to excessive trauma in passage and manipulation of the needle, or they may arise from back-flow of the medication infiltrating and irritating superficial tissues. After-pains are relieved by local heat with an electric pad, hot water bottle, or warm baths followed by gentle massage.

The injecting needle should always be inserted slowly and gently with a minimum of manipulation to avoid traumatizing tissues, especially blood vessels and nerves. Occasionally, when these precautions are not observed, a needle-point is broken and imbedded in the periosteum.

Surgical precautions as to sterility should be exercised at all times.

Aqueous procaine solutions may be used at room temperature, and should be fresh. We do not add adrenalin. Oily preparations are best heated to body temperature to decrease viscosity and enhance their flow. While aqueous solutions may be injected superficially, oily preparations should always be administered deeply.

### MATERIALS

We have prepared our own solutions of sterile procaine hydrochloride, 1 to 2 per cent, in normal saline freshly as needed. When small amounts are injected, up to 20 c.c., the 2 per cent solution is employed. The oily solution we use consists of procaine base, the only oil-soluble form, in sweet almond oil, dissolved in the hot oil after it is sterilized. One half to a 5 c.c. maximum of the oil may be used for injection at any particular site. The larger doses are best employed for divided, fanwise administration about a painful site to avoid undue local reaction. We have studied several of the new local anesthetic agents and a number of our own formulae which are not included in this discussion because our investigations so far are not sufficiently extensive to report.

Rustless steel needles of the beaded hilt, "Security" type should be used. The average gauge for general utility is 22. The length required may be from 1 to 5 inches depending on the place treated. Short hypodermic needles are required, of course, for the preliminary intracutaneous skin wheal at the painful area preceding every deep injection.

The regular, long 2 c.c. and 10 c.c. syringes are adequate. Barrel

flanges are helpful. The Luer lock attachment will serve for the aqueous solutions but makes oil injection difficult.

### BRACHIAL PLEXUS BLOCK FOR THE PAINFUL SHOULDER

The brachial plexus block in painful conditions of the shoulder region with aqueous procaine solution, as indicated in a previous report,<sup>12</sup> proved highly effective. The aqueous preparation seems adequate and its benefits of longer duration in this locality, probably because of the ease with which the medication is deposited at the nerve plexus. Owing to the delicate features of the anatomical structures we have not used the oily substance in this region.

The plexus block has been utilized as a routine measure in all intractable, non-operable disturbances of the shoulder region,—fibrositis, neuritis, bursitis and arthritis. Many painful pathological conditions of the shoulder area dependent on the brachial branches for nerve supply appear to be amenable to this form of therapy. A small percentage of cases are refractory to local procaine infiltration, even with the best technic. Painful acute and chronic involvement of the elbows, wrists and digital joints have been effectively relieved by this route but are not included in our report. We have employed, with slightly modified technic, the supraclavicular block of Labat,<sup>13</sup> as in figure 1.

### PERIARTICULAR INJECTION OF THE KNEE

The knee was one of the most commonly treated sites. As a weight bearing joint, when invaded by arthritic changes, usually osteoarthritis, it is often a source of severe pain. This discomfort arises as a rule from irritated nerve fibers supplying strained or infiltrated periarticular tissues, tendons and ligaments, particularly at their insertions and attachments. Further weakening and relaxation of the fibrous supportive structures of the joint by the intrinsic disease process leads to defective mobility, increases stress and muscle spasm with their attendant malaise.

When injecting the knee, the sore sites are determined by deep pressure against the underlying bone and, at the points of maximum tenderness, intracutaneous wheals are made with aqueous procaine solution. Injection of 2 to 5 c.c. of aqueous procaine solution is then made over, and down to, the bony contact points, usually as indicated in figure 2. If the patient is sufficiently improved, the aqueous solution may be repeated until lasting relief results. If the comfort is too brief, the oily preparation, 1 to 2 c.c. at each site, is given at the next sitting. For complete injection of the joint, we have utilized the seven point scheme of Forestier (figure 2) in 2 to 3 sessions. This method includes all of the likely tender points found about the knee.

Intraarticular injection sometimes occurs by this technic and produces

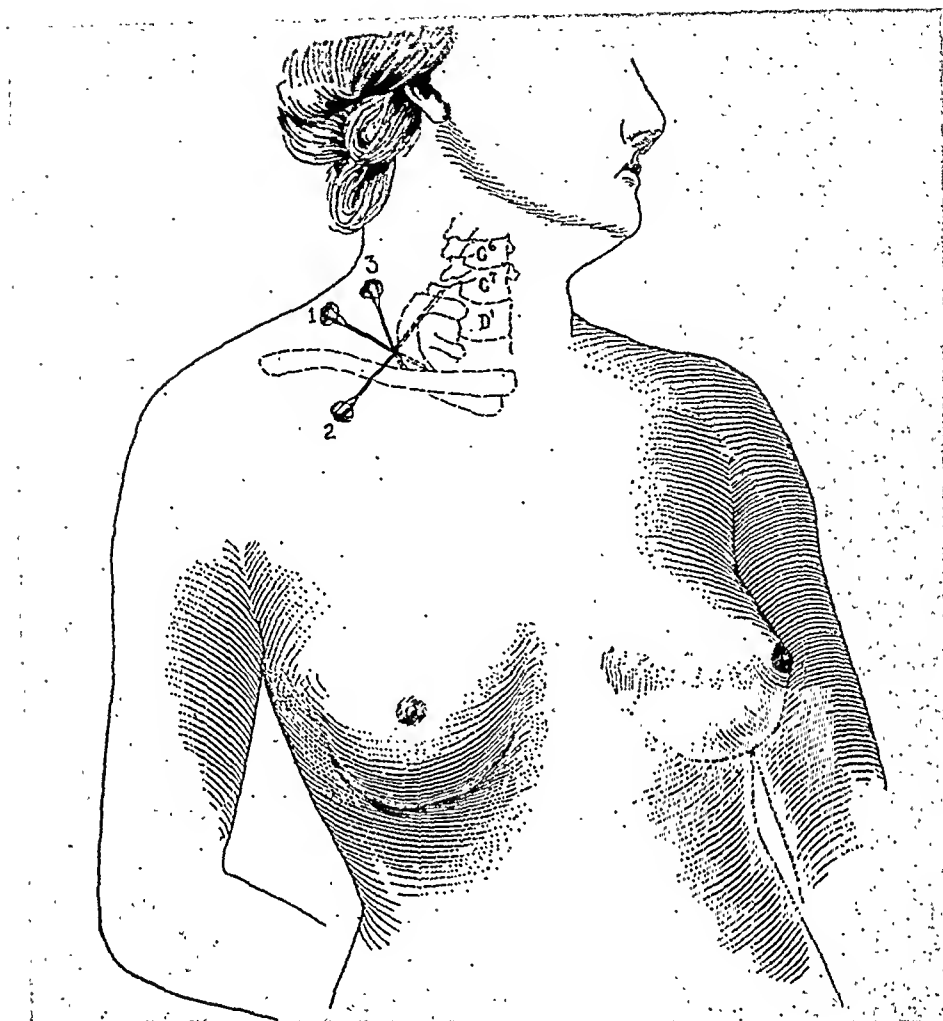


FIG. 1. Brachial plexus block by the supraclavicular route. The three directions of the needle: (1) aims at the first rib; (2) at the transverse process of C<sup>6</sup>; (3) at the posterior margin of the first rib, behind the clavicle. (From Labat, G., *Regional Anesthesia*, Saunders.)

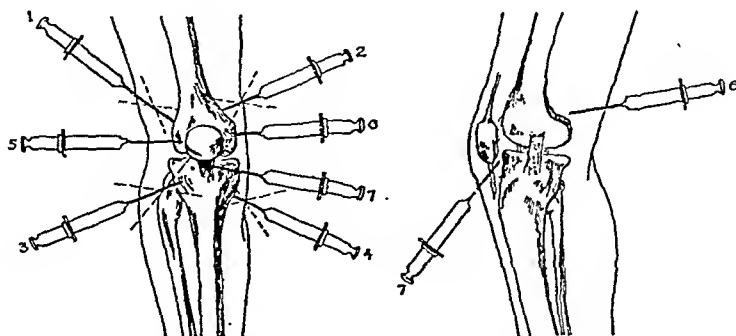


FIG. 2. Numbers 1, 2, 3, 4 and 5 are injected around the joint capsule; number 6 is made in the popliteal fossa near the cruciate ligaments; number 7 is made under the patellar ligaments. (Forestier, J., *South. Med. Jr.*, April, 1935.)

little or no reaction if aqueous procaine solution has been employed. With the oily solution, however, an acute chemical arthritis with signs of inflammation and effusion appears in 6 to 12 hours and subsides in 3 to 6 days ordinarily. The patient should always be warned in advance of this possibility and should be informed of its temporary nature and instructed as to what to do for relief. Our experience with intraarticular therapy with a variety of preparations has demonstrated that some degree of local, and possibly systemic, reaction is likely to follow. Small doses of oil (0.5 c.c.), injected into the knee and gradually increased, were fairly well tolerated by several patients.

### PERIOSSEOUS INJECTIONS

Injections about painful, bony processes, particularly osteoarthritic spurs, are useful when operation is refused or must be deferred. In fact, such procedures might well be utilized as preliminary measures before subjecting some patients to surgery. If sufficient relief is obtained by periodic injection of the painful site, the discomfort eventually may not reappear. Chronic talalgias are injected at the region of the exostosis as indicated by roentgen-ray or fluoroscopy. The osteophyte may be approached from whichever aspect of the foot offers the shortest route. A subcutaneous wheal is made and the needle pierces down to periosteum (figure 3). One-half to 3 c.c. of oily solution are injected at and about the spur, followed by gentle massage for 1 to 2 minutes. There follows a local reaction of tenderness and swelling which may last one to three days and imposes some limitation on walking. Like Forestier,<sup>4</sup> we have observed in some cases gratifying results from medicated oil and aqueous solutions administered for painful hallux valgus and severe metatarsalgias and deposited at the bony seat of pain in these localities (figure 3).

### SACRO-ILIAC REGION

For sacro-iliac pains not responding to the usual measures, local injection is a worthy adjunct. A procaine wheal is made at a point just medial to the margin of the posterior superior iliac spine and the needle is thrust 1 to 3 inches deep until bone is struck. Twenty c.c. of 2 per cent aqueous procaine solution or 5 c.c. of procaine in oil are deposited in three fanwise divided injections into the soft tissues over the joint, as in figure 4 (B).

### PARAVERTEBRAL INJECTIONS

Cervical, dorsal, lumbar, transsacral and caudal injections were employed where definite nerve localization was present. The methods described by Labat<sup>13</sup> were followed. The operator must be properly trained in the technic of these procedures. They constitute the logical and most effective approach in herpes zoster, neuralgia, neuropathy, arthritis of the

spine, metastases to the spine and in any parietal pain not responding to local injection at the painful site. Our experience has proved that repeated paravertebral injections of procaine solution, aqueous or oily, deposited at one or more points will adequately relieve most of the prolonged, painful conditions of selected cases of arthritis and related diseases. Finally, in intractable cases, alcohol injection can still be done by the paravertebral route, or in the extreme situation neurosurgery may be required for relief. Deep roentgen-ray therapy is being employed with favorable results in some intractable neuropathies.<sup>5</sup>

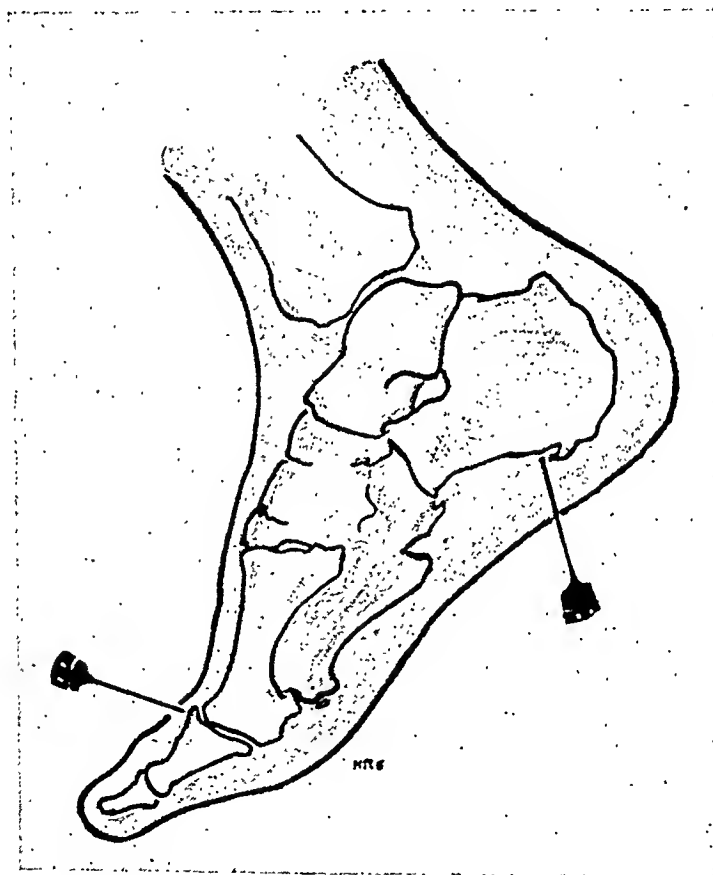


FIG. 3. Method of injecting painful spurs and osteophytes of foot.

### SCIATIC NERVE INJECTION

Large nerves may be injected peripherally. Most commonly the sciatic nerve is involved and in this condition the peripheral, perineural or intra-neural injection is frequently helpful. These procedures are performed preferably at the sciatic foramen. We have employed a modification of the technic described by Strauss<sup>14</sup> and others.

As in figure 4A, the patient lies in a lateral position, the side to be treated uppermost, the higher thigh flexed. A line is drawn joining the posterior superior iliac spine to the greater femoral trochanter at its supero-



posterior prominence. A perpendicular at the midpoint of this line is drawn and at a point  $1\frac{1}{2}$  inches along this perpendicular the injection is given. Following an intradermal wheal, a 4 to 5 inch needle is inserted through skin and muscle directed anteriorly and slightly medially. When the needle pierces the nerve, paresthesia is elicited. Frequently gluteal spasm is a visible accompaniment. Often the needle first impinges on iliac bone. A little gentle manoeuvring of the needle is then required until the nerve sheath is penetrated and paresthesia provoked.

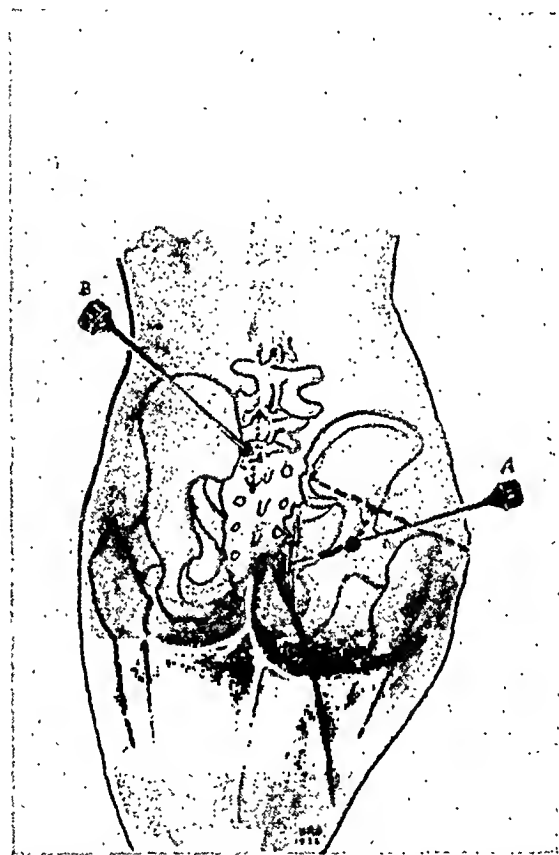


FIG. 4. Needle A indicates site of sciatic nerve injection for perineural or intraneural therapy. Needle B shows method of fanwise injection for pain about the sacro-iliac region.

For intraneural analgesia the solution is injected at this point. For perineural administration the needle is slightly withdrawn, and 10 to 30 c.c. of aqueous 1 to 2 per cent procaine solution, or 5 c.c. of oil, are injected about the nerve area. Good results have been reported from intraneural injections. We prefer the extraneural method ordinarily. When adhesions within the nerve sheath are suspected, intraneural injection of 10 c.c. of procaine, 2 per cent, followed by 50 to 75 c.c. of warm, normal saline may be given effectively.

Caudal injection of aqueous and oily medication has been so amply described in the literature<sup>15</sup> that it will be omitted in this discussion. We have

used the epidural technic in those patients who fail to benefit by peripheral, truncal injection. In a limited number of cases when both of these procedures prove inadequate, paravertebral block of the lumbar and sacral nerves becomes necessary.

### MUSCULAR AND FIBROUS TISSUE INJECTIONS

The site of maximum tenderness is determined by inspection, manipulation, exercise and deep palpation. There may be several areas of preponderant tenderness as shown in figure 8. For effective therapy the examiner must recognize and inject the actual source of pain and radiation, rather than areas of reflex tenderness which are relieved spontaneously when the focal points are blocked. Having determined these points, or the point,

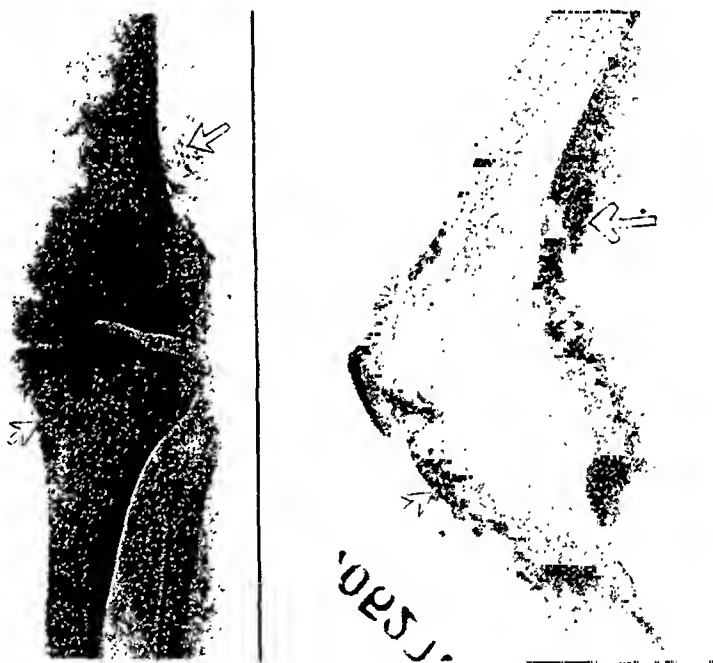


FIG. 5. Periarticular injection of knee at tender points with iodized oil.

for injection, one or more superficial wheals are made, and with a 2 to 3 inch needle, 5 to 20 c.c. of aqueous solution or 1 to 5 c.c. of oil are injected directly into the site of pain and tenderness.

We have found this procedure of great value in traumatic and infectious conditions, especially in fibrositis of the erector spinae, gluteal and thigh muscles; about the fascia lata, lumbo-sacral and sacro-iliac ligaments in back pain. If painful, sharply circumscribed, subcutaneous or intramuscular nodules are palpable, they are penetrated with the needle and 5 to 10 drops of the solution are injected into the center of the nodule, the treatment then being completed with radiating fractional deposits of 3 to 5 c.c. of aqueous or oily solution about and beyond the nodule. If a nodule is persistently

and exquisitely tender, 3 to 6 mm. of 95 per cent alcohol are injected into the nodule and 5 c.c. aqueous solution about the site of pain.

In widespread fibrositic involvement of fascia or muscles, particularly in the gluteal and low back regions, we have resorted to deep, massive injections of 10 c.c. of 2 per cent procaine with 25 to 100 c.c. of normal saline. This method appears to exercise its benefits by breaking up adhesions as well as by the analgesic action of procaine and of volume pressure. Tenderness and crepitation frequently disappear after 1 to 2 such treatments.

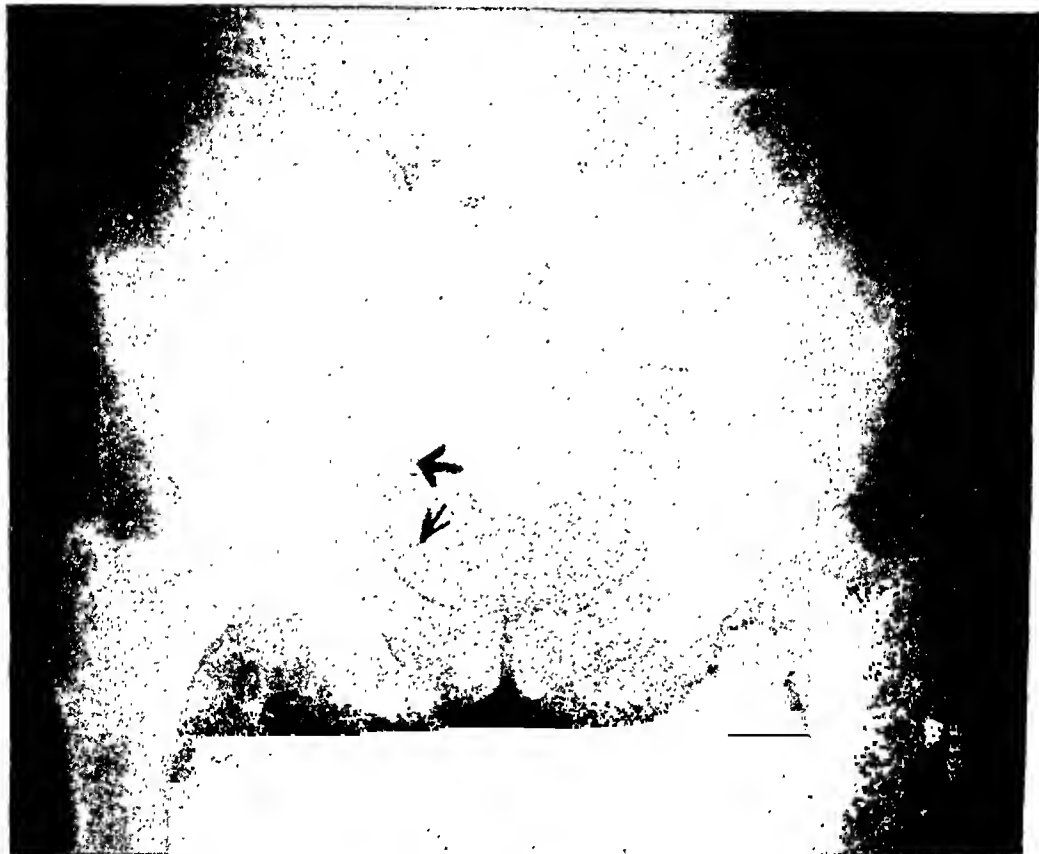


FIG. 6. Perineural and intraneural injection of sciatic nerve with brominized oil.

Relief in acute traumatic and fibrositic ("lumbago") back pain has been reported<sup>18</sup> recently by injection of aqueous procaine solution. In chronic fibrositis, especially with muscular and fascial nodulation, Maliwa<sup>16</sup> advocates the administration of small doses of procaine solution in situ.

#### HAZARDS IN REGIONAL AND LOCAL INJECTIONS

In our experience with several hundred regional and local injections, we have seen only one severe mishap. A patient with known coronary disease, 70 years of age, was given brachial plexus block without proper inquiry into her general condition. Following only the intracutaneous wheal she fainted.

When the patient was studied in the ward, we found that there was a very definite history suggestive of impending coronary occlusion during the morning preceding the treatment. A lesser complication which occurred once was the formation of a sterile chemical abscess over the sacro-iliac region in a lean subject when an irritating, halogenized oil solution was incorrectly injected subcutaneously, practically between skin and bone. The abscess was arrested spontaneously after two aspirations.

Obviously brachial plexus block is subject to the possibility of perforation of any of the adjacent large blood vessels. Occasionally this accident occurs in our hands and appears inconsequential provided repeated aspiration forms part of the operator's technic, so that he recognizes the vascular penetration before the medication is injected. If small amounts of aqueous procaine solution enter a vessel, no complications are likely, since procaine preparations evidently are administered intravenously with impunity.<sup>17</sup> Puncture of apical pleura or lung may occur but has not happened in our experience.

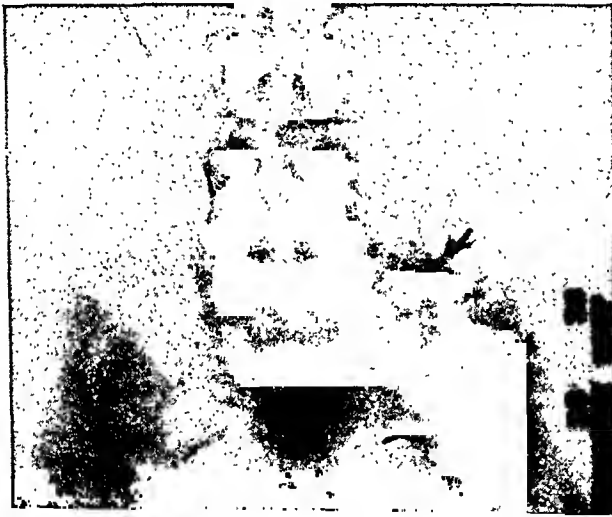


FIG. 7. Sacro-iliac block visualized with brominized oil by fanwise injection.

While we have noted excellent results in some patients receiving intra-articular injection, it strikes us as unnecessary to enter a joint space unless periarticular inoculation has failed to provide relief. We did employ the intraarticular route in some cases of severe osteoarthritis of the knee in which the pathologic changes seemed too far advanced for any added injury to arise. At this time, however, we feel that the arthritic changes produced in animals by introducing into the joints a variety of innocuous substances, including physiological saline and distilled water,<sup>18</sup> should discourage indiscriminate intraarticular instillations excepting in advanced lesions or when a joint must be entered anyhow to remove an effusion.

In the course of perineural and intraneural injection, indelicate technic may lead to injury of nerve tissue, productive of troublesome paresthesia.

Intraneural procedures are usually avoided by us because of this possible hazard. They should be reserved for the large sciatic trunk when intrathecal adhesions are suspected. Employment of large volumes of fluid, with procaine and saline, for intraneural, perineural, intramuscular and extrafascial infiltration, despite their extensive use, appears to be free from the

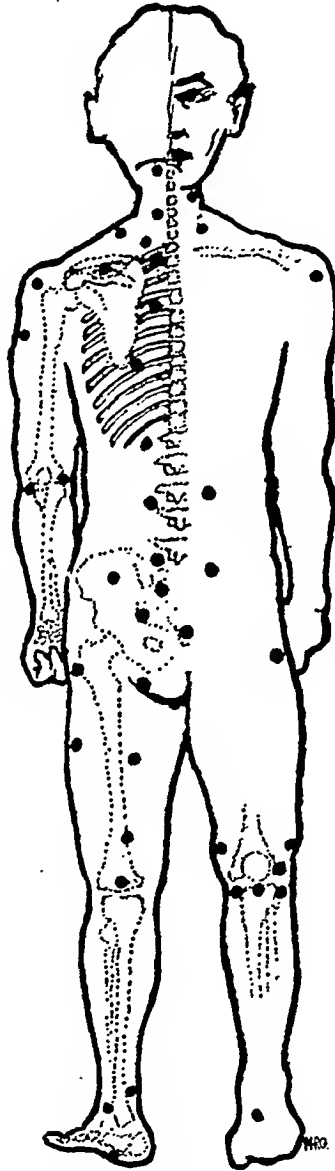


FIG. 8. Common focal points of pain and tenderness on palpation in neuralgic and myalgic (fibrositic) states. At these points local analgesic injection is given.

nerve disturbances reported by Hassin.<sup>19</sup> We have noticed no evidence of persistent infiltration or proliferation at sites repeatedly blocked with procaine solutions. These changes are known to occur following injections of quinine derivatives and were observed by us in five patients who had received such treatment.

## RESULTS

The patients in this study were under our observation from six weeks to eleven months. Almost all of them were coöperative enough to attend our clinic for a minimum period of three months to permit us to watch closely the effects of therapy. In estimating our results we were guided by the subjective relief of pain and stiffness and the objective changes in tenderness, muscle spasm and mobility of the part. Improvement was considered moderate when pain ceased and 50 to 70 per cent recovery of function occurred. Great to complete improvement was evidenced by functional recovery of 70 to 100 per cent as well as by the absence of pain.

As table 1 indicates, the number of patients treated with brachial plexus block for painful shoulder conditions has increased since a preliminary re-

TABLE I  
Results of Local and Regional Injections

No. Cases Treated	Brachial Plexus Block	Direct Bursa Inject.	Para-vertebral Block		Inject. Sciatic Trunk	Intra-artic. Injection		Peri-artic. Inject.	Local Inject. for Fibrositis Low Back
			Proc.	Oil		Proc.	Oil		
134	42	13	12	9	9	13	5	16	15
Unimproved	6	6	2		1	6	2	3	2
Slightly improved	2				2	2		2	
Moderately improved	4			4	2	2	1	2	3
Greatly or entirely improved	30	7	10	5	4	3	2	9	10
Average number injections	5.5	3.3	3.7	1.7	5.2	2	1	5.9	6.7
Duration of disease	2 mos. to 7 yrs.	3 mos. to 8 yrs.	3½ mos. to 7 yrs.	9 wks. to 8 yrs.	9 mos. to 5 yrs.	2½ mos. to 15 yrs.	1-5 yrs.	1-4 yrs.	3 mos. to 4 yrs.

port<sup>12</sup> to 42. This group represents a variety of pathological states; in it 32 patients, or 80.9 per cent, were moderately to entirely relieved; 4.7 per cent only slightly improved, and 14.3 per cent unimproved.

Of 13 patients receiving direct injection into the subdeltoid bursa, seven were improved and six were not benefited. This procedure has not demonstrated in our hands the effectiveness shown by brachial plexus block in bursal disease of the shoulder region.

Intraarticular administration of aqueous procaine solution in the early stages of our clinical investigation failed in seven of 13 patients and gave slight relief in two. Two of five patients receiving the oily solution showed great improvement.

Periarticular injection, chiefly of the knee joint, elicited complete or

moderate improvement in 11 of 16 patients, slight improvement in two and none in three patients. .

Perineural deposit of solution at the sciatic trunk in nine patients gave complete improvement in four, slight benefit in two patients and none in another. Two patients were moderately improved.

Local injection for fibrositis was performed in 15 patients, all with involvement of the low back or gluteal areas. Ten cases responded with great or complete improvement, three were moderately benefited, while two patients were unrelieved.

Paravertebral block proved greatly or completely effective in 10 of 12 patients receiving aqueous procaine solution. Of nine patients treated with the oily preparation all were moderately, greatly or completely benefited. The paravertebral route was the most effective approach employed in this study. It appears to be, on anatomical, physiological and anesthetic principles, the most useful procedure for relief of the painful conditions presented here. We have employed the peripheral methods of injection at some pain sites, as previously stated, in order to evaluate their utility. The peripheral, local injection requiring no specially trained technic and offering a simple approach, nevertheless, may often prove, according to our results, a valuable adjunct in the management of arthralgia and related painful states.

The series of 134 patients showed great or complete improvement in 59.7 per cent, moderate improvement in 13.4 per cent, slight improvement in 5.9 per cent, no improvement in 20.9 per cent. Of the latter group of (28) unimproved patients, nine failed to appear after the first treatment. While we have had a number of recoveries following one injection, we considered treatments as failures, for the sake of conservative evaluation, if the patient failed to return for further injections or follow-up after the first block.

The average number of injections varied with the locality treated as shown in table 1. A limited number of patients were injected at some sites. We feel that inclusion of these small groups in our study is justified by the fact that we are reporting the results of the application of basic principles common to all of the treatments at the various locations.

It is interesting to note that only two patients presented such severe symptoms, unresponsive to procaine analgesia, that paravertebral block with alcohol was required and was permitted. Our experience suggests that the pain in arthritic and allied conditions, even when protracted and severe, yields frequently to repeated procaine injection.

The patients reported in this series usually were given no other form of analgesic therapy in order that the results of block treatment could be properly evaluated. Undoubtedly, as we have observed in our private patients, when these analgesic procedures supplement suitable medical, physiotherapeutic and orthopedic measures, as they should under ordinary circumstances, a smoother, briefer period of treatment may be expected. Manipulation and local supportive devices such as bandages and casts are tolerated better, and

prove more effective, when applied after injection therapy in these painful states. We must emphasize that analgesic injection therapy should be employed only as an accessory to the accepted medical and orthopedic management of these conditions.

### FOLLOW-UP

During preparation of this article an effort was made to obtain a report of progress by mail or by reexamination of the patients in our study. In most of the series included here, treatment was completed from 4 months to 2½ years before compilation. We succeeded in getting acceptable information or a return visit from 19 patients. Of eight who had received brachial plexus block for shoulder conditions four months to two and one-half years earlier, all reported satisfactory and continued relief. One of these patients occasionally is subject to bouts of shoulder pain unaccompanied by disability. Two continued to have diffuse aches elsewhere, just as they did before treatment.

Of seven patients receiving periarticular injections of the knee, ten months to two years prior to our inquiry, three appeared to have continuous adequate to complete relief. Two patients, one who received periarticular procaine in oil injection of the knee eight months before reexamination, and another who was given periarticular procaine solution three years previously, reported the same pain and disability without any improvement at any time following therapy. Two patients, treated with paravertebral procaine in oil six months and 18 months respectively before follow-up, reported persistent, complete relief.

One patient, given three perineural procaine solution injections of the sciatic nerve, after one year stated that she had felt no return of the symptoms which had been disabling for six months before nerve blocking. Following the injections, she had experienced from time to time occasional twinges of "muscular" pain but none in the region of the sciatic distribution. One patient who received two injections about a painful spur of the os calcis reported complete freedom from pain and disability at the time, five months after treatment.

Of the 19 patients answering or returning, 17, or about 90 per cent, therefore, appeared to be adequately or completely relieved of the intractable pain and disability for which they had required treatment. The intervals between treatment and check-up varied from four to 30 months. Two patients had obtained no relief immediately after injection, both receiving periarticular therapy of the knees. One was a female of 76 years with advanced osteoarthritis; the other was a male of 60 years with a severe post-traumatic and osteoarthritic condition of the treated knee of many years' duration complicated by long-standing fibrous ankylosis. Four patients who had experienced complete relief following local injections reported severe, periodic pain in other parts of the body but complete, lasting quiescence of the area treated.



## DISCUSSION

The patients reported here were treated at different painful sites for a variety of conditions, but the methods of relief were essentially identical. Our observations demonstrate, so far, that in chronic arthritis and related disease presenting prolonged, intractable discomfort, local or regional analgesic therapy offers relief, rest and relaxation for a majority of the patients.

While the treatment described is essentially palliative, the enduring relief of pain and general improvement often resulting from repeated local and regional injections of procaine solution raise the question as to the basis of the lasting response to what is expected to be transient medication. The clinical course of patients under treatment suggests a number of direct and indirect beneficial effects of regional and local analgesia.

An immediate reaction to procaine solution is, obviously, anesthesia. We have been impressed by the striking persistence of analgesia in many of these painful states after anesthesia has disappeared. With oily solutions of procaine, prolonged analgesia is especially noticeable. These observations have been confirmed by Bacon<sup>20</sup> of Philadelphia who has injected oil-soluble anesthetics caudally and transsacally for rectal neoplasms and obtained 1 to 2 weeks' relief of pain when roentgen-ray and radium had failed to give adequate control of discomfort.

Another direct effect of local analgesic injection is probably a hyperemia contributed in part by the vasodilatation arising from the pharmacologic action of procaine with its anesthetization of any immediate sympathetic nerve supply. It is likely also that the injections act as a form of regional shock therapy with a local foreign body reaction and congestive response that add to the hyperemia.

Another important feature of these therapeutic injections is the relaxation of reflex muscular spasm and prevention of atrophy following the resulting disuse when prolonged. The release of spasm sometimes appears immediately after treatment and becomes more pronounced and maintained as the injections are repeated. Abnormal postural tendencies are to some extent corrected reflexly following relief. Further functional improvement is afforded by the manipulative procedures which then are permitted. Normal mobility becomes possible in many cases where joint function had been limited for some time. Systemic response to eradication of pain and local relaxation is evidenced by the improved well-being of the patient, allowing rest and sleep which frequently are disturbed. The patient's outlook and morale are stimulated by what is often the first appreciable relief in an extended period of discomfort and disability.

These observations concerning the effects of analgesic block on reflex, spastic, and eventually atrophic, changes associated with such prolonged, painful states are supported by the work of Reymond<sup>21</sup> years ago. As May<sup>21</sup> reports, "by injecting silver nitrate and turpentine into the knee joints of dogs, he (Reymond) produced suppurative arthritis and noted the

appearance of the atrophic changes and exaggerated reflexes associated with the chronic arthritis of humans. However, muscular atrophy requires for its production an intact reflex arc; if it is broken, he found, for example by sectioning the posterior roots, muscular atrophy does not occur." Local analgesia permits a temporary interruption of the sensory reflex at the painful, involved area.

An added source of benefit upon which we may speculate is the probable elevation, or modification, of the threshold of pain in these patients when prolonged or repeated analgesia is introduced. This change in the sensory response may be influenced by the repeated interruption of the prolonged pain-spasm cycle, as Reymond's work suggests. By a reduction in the number of pain stimuli transmitted from the pathological site after analgesic therapy, interference with the "summation of stimuli"<sup>22</sup> characteristic of these prolonged painful states may occur. Furthermore, some effect upon the local tissue metabolism may well be initiated by the local analgesia, hyperemia and rest.

There are mechanical effects of local injections which probably play a part in the improvement achieved. The administration of large volumes of fluid, by separating contiguous tissues and stretching or breaking fine adhesions, may add to the intrinsic value of the medication, especially in fibrositis and in periarticular pathologic lesions. When the oily solutions are employed, there may be some further lubricant value in such a medium, probably at the movable surfaces of muscles, bursae, tendons and joint structures where palpable crepitation suggests roughening of adjacent tissues.

In the disorders considered here, the well-known tendency of long inactive joints and muscles toward disuse atrophy is commonly observed. Whether the patient actually feels pain on movement or merely fears pain, mobilization of these structures often can be induced for the first time and maintained by local or regional analgesia with procaine solutions. Certainly in protracted, painful articular and related disorders, when they fail to respond to the usual methods of management, a form of treatment frequently offering lasting relief of discomfort and its associated disability should prove a worthy adjunct to our therapeutic resources. The effectiveness of local and regional analgesic injection in our group so far warrants more extensive clinical and other investigation of this form of therapy in painful, disabling rheumatic disease.

The chief limitation of local and regional analgesia at the present time, apart from paravertebral alcohol block, is the necessity in many patients of repeated injection in order to maintain prolonged relief of pain until adequate recovery is accomplished. The present trend in the development of local anesthetics promises in the near future the production of an agent with the advantages of prolonged analgesia and low toxicity. When such a substance becomes available and is applied by the various technics discussed, we will have a potent remedy requiring fewer injections for the control of

disabling pain in a still higher percentage of arthritics than we are able to report at this time. As a last resort, for the present, in those situations where milder analgesia is ineffective or requires too frequent repetition, there still remains alcohol block of the nerve supply to the painful part by the paravertebral route.

### CONCLUSIONS

We are aware of the tendency of rheumatic disease to show spontaneous remissions. Since almost all of the patients, however, had received for some time previously other accepted measures without relief, this previous period of therapy was available in these cases as a control. The follow-up information, even though limited to 19 cases, indicates at least that the immediate relief offered by local and regional injections is sustained for long intervals in many of the patients. More precise evaluation will have to await further lapse of time and additional experience with these procedures. Therapy was more effective at some sites than at others, due, we believe, to varying difficulties of technic at different areas. From our observations in the treatment of the group reported here and from the information elicited by our follow-up study, the following conclusions may be stated:

(1) Repeated injection with aqueous and oily solutions of procaine according to accepted anesthetic methods, at the site of pain or at the source of nerve supply to the painful area in a group of 134 patients with chronic, intractable discomfort, gave poor, or no, results in 20.9 per cent of the patients; slight improvement in 5.9 per cent; moderate relief in 13.4 per cent and complete, lasting relief of pain in 59.7 per cent of the patients, a total of 73.1 per cent of the patients experiencing moderate to complete relief.

(2) Follow-up of 19 patients from 4 to 30 months after treatment revealed 17 still adequately or completely relieved; two unrelieved.

(3) The treatment of intractable arthralgia and allied painful states by local or regional analgesic injection offers a promising, palliative, accessory therapeutic measure in arthritis and related conditions.

TABLE II

	Number of Patients	Percentage
Unimproved.....	28	20.9
Slightly improved.....	8	5.9
Moderately improved.....	18	13.4
Greatly improved or fully recovered.....	80	59.7
Total patients treated.....	134	
Total, slight or no improvement.....	36	26.8
Total moderately to entirely improved.....	87	73.1

I wish to acknowledge the assistance in the conduct of this study given by the staffs of the Arthritis Clinics of the N. Y. Post-Graduate Medical School and Hospital and of Bellevue Hospital, 4th Division, particularly by Drs. Freeman Brooks, Edward E. P. La Motta, Saul Solomon and James M. Tarsy. Figures 3, 4, and 8 were drawn by Harry R. Greenburgh, D.D.S. Special preparations were supplied by Abbott Laboratories, Rare Chemicals, Inc. and E. R. Squibb and Sons.

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# THE SIGNIFICANCE OF GASTRIC ACIDITY AFTER HISTAMINE STIMULATION: A STATISTICAL STUDY OF 2877 GASTRIC ANALYSES\*

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MOST of the reports of gastric analyses which have appeared previously in the literature<sup>1, 2, 3</sup> are based upon values obtained after a test meal of the Ewald type. It is well known that the administration of histamine is the most reliable method of evoking gastric secretion.<sup>4, 5</sup> Since the opening of Duke Hospital in 1930 all gastric analyses here have been made with the use of this drug, and examinations of the contents of the stomach by this method have been made in 3675 patients. It seems profitable, therefore, to examine these data critically in order to determine whether acid values obtained with histamine stimulation vary materially from those obtained with the Ewald meal, and to evaluate, if possible, the significance of a single gastric analysis in the diagnosis of disease.

*Method of Gastric Analysis.* In all patients in this series the gastric analysis was done according to the following routine:

1. Fasting contents were withdrawn from the stomach.
2. 50 c.c. of 7 per cent ethyl alcohol were then given to the patient by mouth.
3. 0.5 mg. of histamine acid phosphate was given subcutaneously.
4. At the end of 45 minutes the contents of the stomach were withdrawn and titrated against N/10 NaOH, using Töpfer's reagent and phenolphthalein. The analysis of free acid only is reported.

*Material.* This study is based upon the acid values obtained in 2877 patients. Of this group, 1917 patients showed no evidence of disease after thorough study, *including a roentgenological examination of the gastrointestinal tract.* These were used as normal controls. The analyses in those patients who had no roentgenological studies were discarded, even though there was no clinical evidence of disease. It is believed, therefore, that those patients classified as normal controls actually had no organic disease. All patients with systemic disease, such as syphilis, tuberculosis, hypertension, nephritis, and heart disease were excluded, and the results of gastric analyses in the following disease groups were selected for study: *duodenal ulcer, gastric ulcer, carcinoma of the stomach, chronic cholecystitis, pellagra, rheumatoid arthritis, and hypertrophic arthritis.* The diagnosis of

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duodenal or gastric ulcer, gastric carcinoma and chronic cholecystitis was confirmed in every case by roentgenological studies or by operation.

The distribution of the data under consideration is summarized in table 1. Since the analysis is concerned with the acid values of patients showing free acid, all patients with achlorhydria will be considered separately.

TABLE I  
Distribution of Cases

	Number Showing Free HCl	Number With Achlorhydria		Total
		No.	%	
Normal controls.....	1706	211	11.0	1917
Duodenal ulcer.....	419	24	5.4	443
Gastric ulcer.....	42	3	6.7	45
Carcinoma of stomach.....	37	48	56.5	85
Chronic cholecystitis.....	92	38	29.2	130
Pellagra.....	53	50	48.5	103
Rheumatoid arthritis.....	51	9	15.0	60
Hypertrophic arthritis.....	79	15	16.0	94
TOTALS.....	2479	398		2877

*Range of Free HCl in Normal Controls.* Tables 2 and 2a summarize the findings in this group according to age and sex. The number of cases in each decade was plotted against the acidity and tabulated as shown. The arithmetical means, the standard deviations from the mean and the coefficients of variation are included. The wide range in values is indicated not only by the figures in the distribution table but also by the large coefficients of variation. In two-thirds of the analyses the acid values range from 30 degrees to 85 degrees of acidity. This is shown graphically in chart 1. In the remaining cases the acid values fell outside of this wide range.

As seen in the tables and chart, the mean for females is lower than that for males for corresponding decades. This has been pointed out by Vanzant.<sup>1</sup> To determine whether this difference was significant the usual statistical methods<sup>6</sup> were employed, and the results are shown in table 3. Significant differences were found in all decades studied except in the sixth and seventh.

*Gastric Acidity in Certain Diseases.* The gastric acid values found in different diseases were grouped and compared with the normal standards established above. Since the number of cases in each group was relatively small, the calculations used in making table 3 were not directly applicable, and the following method, which takes into consideration both age and sex, was employed. The gastric acidity of each case was compared with the mean for the corresponding decade and sex. These positive and negative



TABLE II

Distribution of Cases in Normal Controls According to Age and Sex—Males Age

Gastric Acidity	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	Total	Per-centage
1-10°		3	7	14	7	7				38	4.5
11-20°		3	14	17	10	8	4	2	1	59	7.0
21-30°		1	16	13	9	12	1			52	6.2
31-40°		7	26	34	14	8	9	1		99	11.8
41-50°		4	31	29	30	16	8			118	14.0
51-60°		6	26	30	27	11	6	3		109	13.0
61-70°		6	32	29	29	15	2			113	13.4
71-80°		3	28	36	16	10	2	1		96	11.4
81-90°		6	17	19	14	17	3	2		78	9.3
91-100°		4	9	14	12	7	2	1		49	5.8
101-110°		2	6	3	8	3	1			23	2.7
111-120°			2	1	3		2			8	0.9
121-130°											
TOTAL		45	214	239	179	114	40	10	1	842	
Mean.....		58.2	55.9	54.0	58.8	55.4	54.0				
Standard deviation...		27.9	22.3	25.6	25.1	28.9	26.6				
Coefficient of variation...		42	40	47	43	52	49				

TABLE IIa

Distribution of Cases in Normal Controls According to Age and Sex—Females Age

Gastric Acidity	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	Total	Per-centage
1-10°		4	8	10	11	8	7			48	5.6
11-20°	1	4	17	22	21	15	9			89	10.3
21-30°	1	2	22	27	17	13	6			88	10.2
31-40°		3	27	34	27	27	8	2		128	14.8
41-50°		8	32	36	31	15	4			126	14.6
51-60°		5	40	38	20	23	6	3		135	15.6
61-70°	1	3	20	28	28	9	3			92	10.6
71-80°		3	11	12	13	20	3			62	7.2
81-90°			8	14	15	14	1			52	6.0
91-100°		1		5	10	2	7			25	2.9
101-110°			3	2	3	3	3			14	1.6
111-120°			1	2	1					4	0.5
121-130°							1			1	
TOTAL	3	33	189	230	197	149	58	5		864	
Mean.....		42.9	46.3	47.4	50.4	49.6	45.5				
Standard deviation...		23.1	26.2	27.7	25.9	25.2	31.3				
Coefficient of variation...		54	59	58	51	51	69				

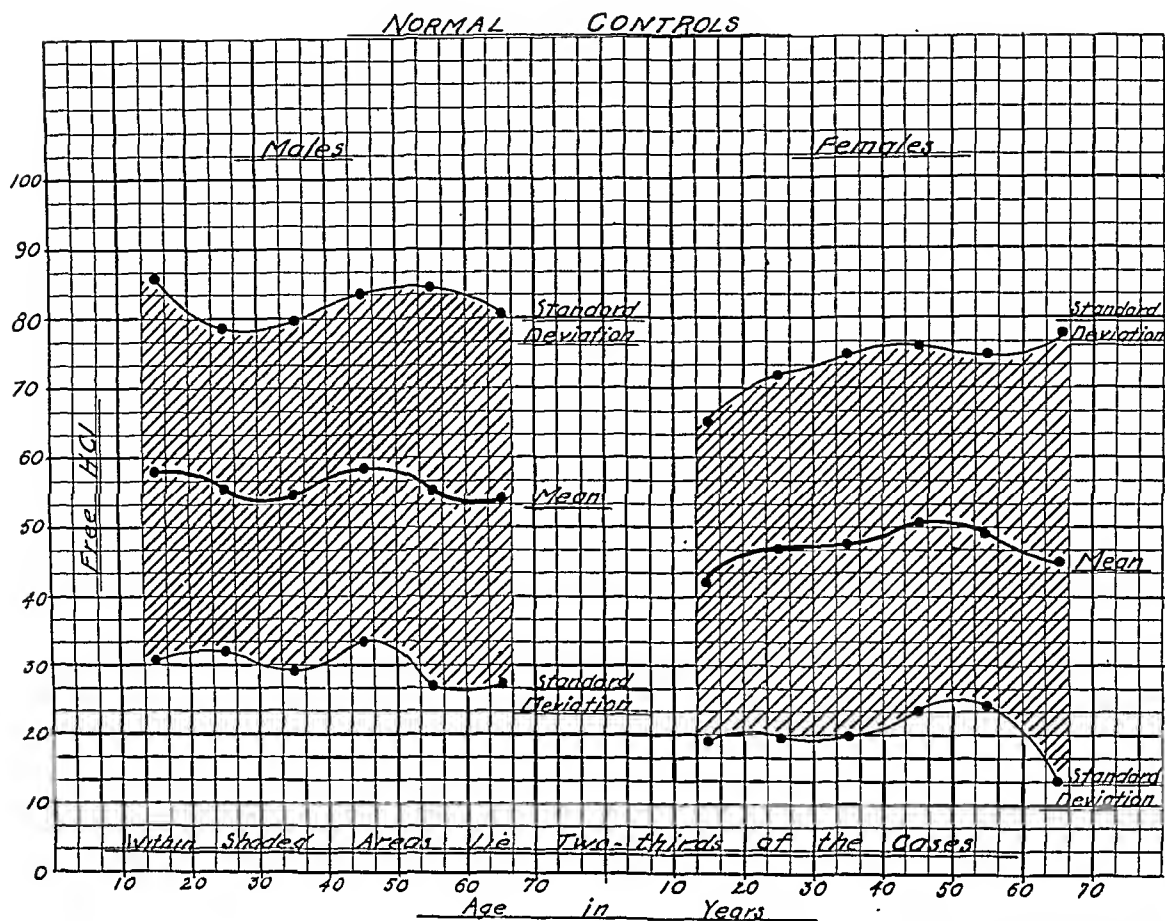


CHART 1

TABLE III  
Comparison of Normal Males and Females

Age	Males			Females			Difference of Mean	Standard Error of Difference	Significance*	
	Mean	Standard Deviation	Number of Cases	Mean	Standard Deviation	Number of Cases				
11-20	58.2	27.9	45	42.9	23.1	33	15.3	5.8	2.6	Significant
21-30	55.9	22.3	214	46.3	26.2	189	9.6	2.4	4.0	Significant
31-40	54.0	25.6	239	47.4	27.7	230	6.6	2.5	2.6	Significant
41-50	58.8	25.1	179	50.4	25.9	197	8.4	2.6	3.2	Significant
51-60	55.4	28.9	114	49.6	25.2	149	5.8	3.4	1.7	Not significant
61-70	54.0	26.6	40	45.5	31.3	58	8.5	5.9	1.4	Not significant

\* The figures in this column were obtained by dividing the difference of the mean by the standard error of the difference. If the value obtained is greater than 2, the difference of the means is significant as indicated in the last column.

differences were totalled. The difference of these totals was divided by the number of cases, giving the mean difference for the disease under consideration. The standard deviation of this difference was then computed and the standard error of the deviation. The results of these calculations are recorded in table 4. It will be observed that a significant variation from the

TABLE IV  
Comparison of Gastric Acidity in Disease with Normal Controls

	Number of Cases	Mean Difference From Normal	Standard Deviation of Difference	Standard Error of Standard Deviation	Significance*	
Duodenal ulcer . . . . .	419	+10.2	25.2	1.2	8.3	Significant
Gastric ulcer . . . . .	42	- 7.3	21.8	3.4	2.1	Significant (?)
Carcinoma of stomach . . .	37	-23.2	32.3	5.3	4.3	Significant
Chronic cholecystitis . . .	92	- 1.4	26.2	2.7	0.5	Not significant
Pellagra . . . . .	53	-12.2	25.3	3.5	3.5	Significant
Rheumatoid arthritis . . .	51	- 2.5	22.8	3.2	0.8	Not significant
Hypertrophic arthritis . . .	79	+ 1.2	28.0	3.1	0.4	Not significant

\* See footnote of table 3.

normal was found in duodenal ulcer, carcinoma of the stomach and pellagra, but not in chronic cholecystitis, rheumatoid and hypertrophic arthritis. In duodenal ulcer only was the level of gastric acidity higher than the calculated normal; in the other diseases it was lower.

*Achlorhydria.* Patients showing an absence of free HCl, excluded from the group of patients studied above, were next considered. The number of patients in each group showing achlorhydria and the percentage of the total are shown in table 1. To analyze this material further, the incidence of achlorhydria in normal controls was determined for each decade and recorded in table 5. The incidence of achlorhydria in the diseases studied,

TABLE V  
Achlorhydria

Males			Females		
Age	Number of Cases	Percentage	Age	Number of Cases	Percentage
0-10	0	0	0-10	0	0
11-20	0	0	11-20	0	0
21-30	10	4.5	21-30	7	3.6
31-40	21	8.4	31-40	20	8.0
41-50	27	13.1	41-50	29	12.8
51-60	32	21.9	51-60	27	15.3
61-80	18	26.5	61-80	20	24.1

shown graphically in chart 2, is highest in carcinoma of the stomach and in pellagra. It will be noted that when free HCl does occur in these diseases, the values are low. Exactly the opposite is seen in duodenal ulcer where there is a high level of gastric acidity and a low incidence of achlorhydria.

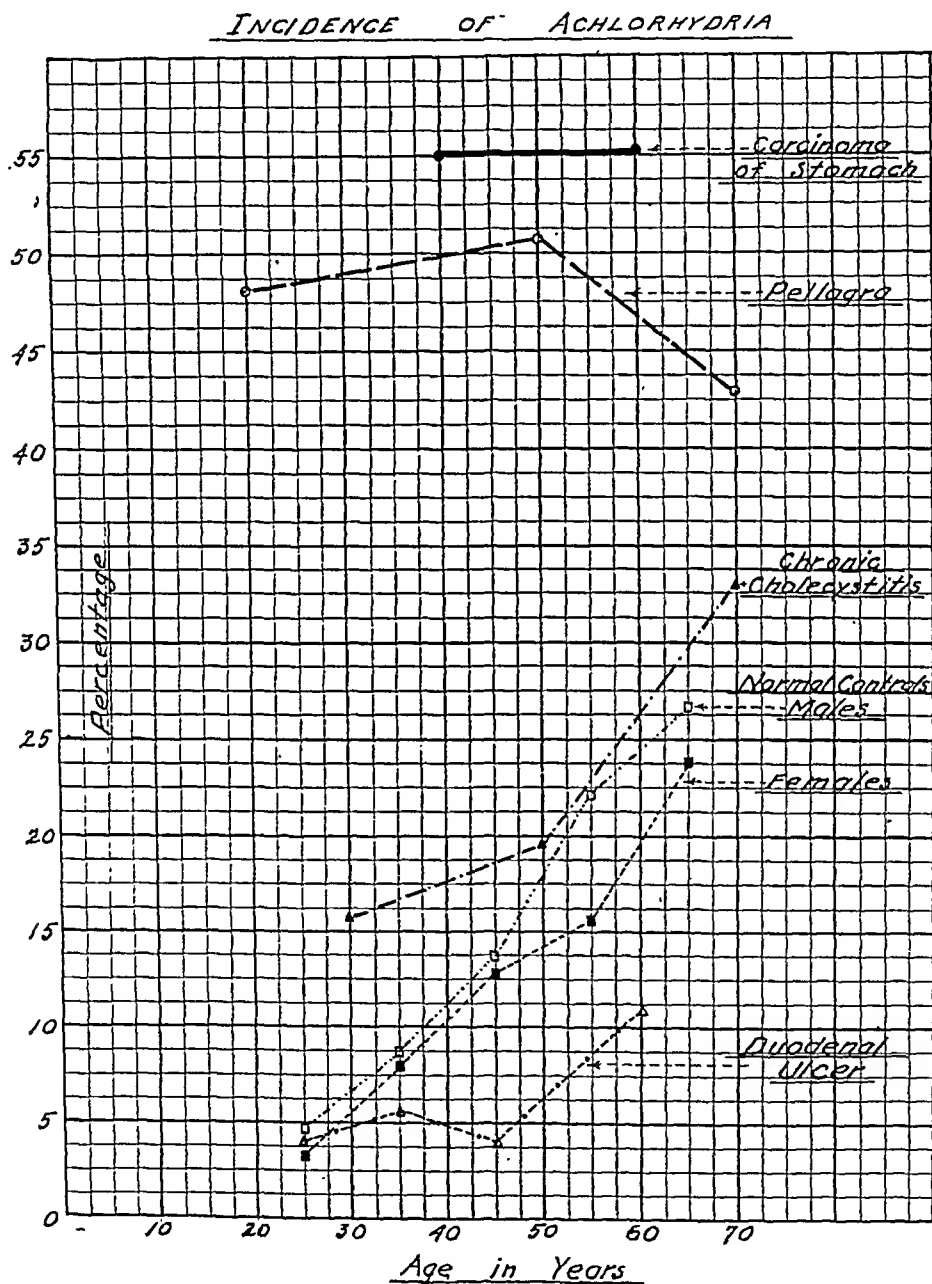


CHART 2

## DISCUSSION

In most hospitals and clinics in this country an analysis of the stomach contents is a routine procedure, rarely omitted in the study of patients presenting symptoms referable to the gastrointestinal tract. Great stress

has been laid upon the amount of free HCl present. There has been some confusion as to just what values are to be taken as evidence of hyper- or hypo-acidity, but in general it is thought that the level of gastric acidity is of definite importance and a material aid in the diagnosis of disease.

In considering the excellent work of Vanzant and her co-workers<sup>1</sup> in establishing the normal range of gastric acidity from youth to old age, it should be pointed out that her findings are based entirely upon values obtained after the use of the Ewald type meal. In this study, on the contrary, histamine was used exclusively. It is interesting to note the close similarity in the results of these separate studies. The incidence of achlorhydria in normals in this study closely parallels that reported by her. It should be pointed out, however, that there is a much wider range of variation in normal individuals after histamine than after the Ewald meal.

From this study it is evident that one cannot assert that there is a normal level of gastric acidity. The range is far too great. As seen in chart 1, a variation of 55 degrés is found in two-thirds of the normal cases, and, of course, a much larger variation exists when all analyses are included. With such a wide range of values occurring in normal individuals, to attach any significance to the actual value of a single determination is not justifiable.

On the other hand, it is evident that a significant difference occurs between the acid values of men and women when a large number of cases is considered. Decade for decade, the mean for women is significantly lower. This does not mean that in an individual case one will necessarily find a lower value for a woman than for a man of corresponding age, but it is probable that this will be the case.

This same reasoning applies equally forcibly to the findings in the diseases studied. In duodenal ulcer it is probable that the acid value will be high; in carcinoma of the stomach and in pellagra one may reasonably expect the values to be low. However, it is clear that a high acid value may occur in either of these diseases, or a low one in duodenal ulcer.

It has been reported<sup>2</sup> that one finds low gastric acidities in rheumatoid arthritis. Referring to table 4, it will be seen that no significant variation from the normal was found in either rheumatoid or hypertrophic arthritis.

The incidence of achlorhydria is interesting. This has been shown by Vanzant to increase rapidly with age. The incidence in the normal controls in this series compares closely with her findings. As one would expect, the incidence of achlorhydria in carcinoma of the stomach and in pellagra is very high. It is frequently stated that achlorhydria does not occur in duodenal ulcer.<sup>4</sup> In this study, 24 patients (5.4 per cent) with active duodenal ulcer, proved roentgenologically, were found to have no free HCl after histamine.

Even though it has been shown that the level of free acid in a single determination is of little significance, one should not draw the conclusion that gastric analyses are useless or should be abandoned. The demonstration of achlorhydria is of sufficient importance to justify the procedure.

## CONCLUSIONS

1. The range of gastric acidity after histamine stimulation in normal individuals is so great that it is impossible to determine what values are to be taken as evidence of normal acidity, hyper-, or hypo-acidity.

2. This range of values is much greater after histamine than after the Ewald meal.

3. If free HCl is present after histamine stimulation, the actual level of acidity is of little, if any, diagnostic significance.

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# THE VALUE OF THE WELTMANN SERUM COAGULATION REACTION AS A LABORATORY DIAGNOSTIC AID; COMPARISON WITH THE SEDIMENTATION RATE\*

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## INTRODUCTION

IN this report we wish to call attention to a nonspecific laboratory test which merits consideration and which we believe is often of more value than the sedimentation rate. This test, which is known as Weltmann's serum-coagulation reaction or the coagulation band of the serum, was proposed in 1930, and has attracted much favorable comment in Europe, although it has not received sufficient trial in this country. Weltmann<sup>1</sup> showed that by this reaction one could distinguish between exudative processes on the one hand and fibrotic processes or parenchymal liver damage on the other. Furthermore, the test is roughly quantitative and reflects the degree of exudation present.

Weltmann found that normal serum which is diluted 50 times with distilled water and then heated in a boiling water bath fails to coagulate, since the minimal concentration of electrolyte necessary for heat coagulation is not present. If sufficient electrolyte in the form of the chlorides of calcium, barium or magnesium is added to the diluted serum, it will then coagulate when heated. In certain conditions the serum was found to require greater concentrations of electrolyte than normal, whereas in others it coagulated with even smaller concentrations than normal. From these observations Weltmann evolved the following technic for his test.

## TECHNIC

A stock solution of 10 per cent  $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$  is prepared and from this, 10 dilutions are made up consisting of 0.1 per cent, 0.09 per cent, 0.08 per cent, 0.07 per cent, 0.06 per cent, 0.05 per cent, 0.04 per cent, 0.03 per cent, 0.02 per cent and 0.01 per cent calcium chloride. Ten small test tubes are placed in a rack and numbered in order from 1 to 10. Into each tube is pipetted 5 c.c. of the similarly numbered  $\text{CaCl}_2$  solution and 0.1 c.c. of hemoglobin-free serum. The tubes are shaken and placed in a boiling water bath for 15 minutes. They are then removed and the tubes which show

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coagulation or flocculation are noted. Coagulation always begins in the tubes with the higher concentrations of calcium chloride and stops toward the lower concentrations. That is, if there is coagulation in the fifth tube, for example, there will necessarily be coagulation in the first four tubes. The number of tubes in which coagulation occurs gives us the coagulation band of the serum. There is usually a sharp unmistakable differentiation between the last tube which shows coagulation and the next tube which may be only turbid or cloudy. Sometimes, however, there is a slight or doubtful coagulation in the intermediate tube and in such cases the coagulation band is said to be between that tube and the one before it. For example, if tube 6 has a definite coagulation and tube 8 has none, but tube 7 has a slight coagulation, the coagulation band is  $6\frac{1}{2}$ . In normal serum the first six tubes usually show coagulation so that the normal coagulation band is 6. If the coagulation band is less than 6 the reaction shows a shift to the left, whereas if the coagulation band is greater than 6, there is a shift to the right.

#### INTERPRETATION OF THE WELTMANN REACTION

In pathological conditions the coagulation band may be normal, shortened or lengthened. Inflammatory and exudative processes were shown by Weltmann to cause a shift to the left or shortening of the coagulation band, whereas fibrotic processes and those conditions associated with parenchymal damage of the liver cause a lengthening of the coagulation band or a shift to the right. In certain instances such as tuberculosis, exudation and fibrosis may occur together and then the coagulation band may be normal, or reflect the predominant process. Hepatic damage may occur together with a severe exudative process such as is sometimes seen in lobar pneumonia, and in such cases the shift to the left which occurs as a result of the pneumonia may be partially offset by the liver damage which by itself would produce a shift to the right.

Although there have been many publications concerning the Weltmann reaction, all but one have been in the non-English foreign literature. Kraemer's <sup>2</sup> report was the first in this country, but he concerned himself only with the use of the Weltmann reaction in diseases of the liver. Foreign workers, particularly those in Germany, are enthusiastic about the possibilities of the test as a diagnostic and prognostic aid.

We have studied the Weltmann reaction in over 2,000 cases of various diseases and have simultaneously compared it with the sedimentation rate in a number of instances. In some conditions, especially tuberculosis, acute rheumatic fever and lobar pneumonia, the coagulation band and the sedimentation rate were repeatedly determined in the same individuals over long periods of time.



## MATERIAL STUDIED

Our material consists of patients admitted to the Cook County Hospital, the Research and Educational Hospital, and some seen in private practice. If a definite diagnosis could not be made either clinically or at autopsy, the case was discarded from our series. Weltmann's original technic was used for determining the coagulation band, and the sedimentation rate was determined by the method of Wintrobe and Landsberg.<sup>3</sup> At the beginning of the work Linzenmeier's<sup>4</sup> method was used, but it soon became evident that for accurate comparisons, corrections should be made for anemia. This was especially true for cases of tuberculosis and sepsis. Also in some con-

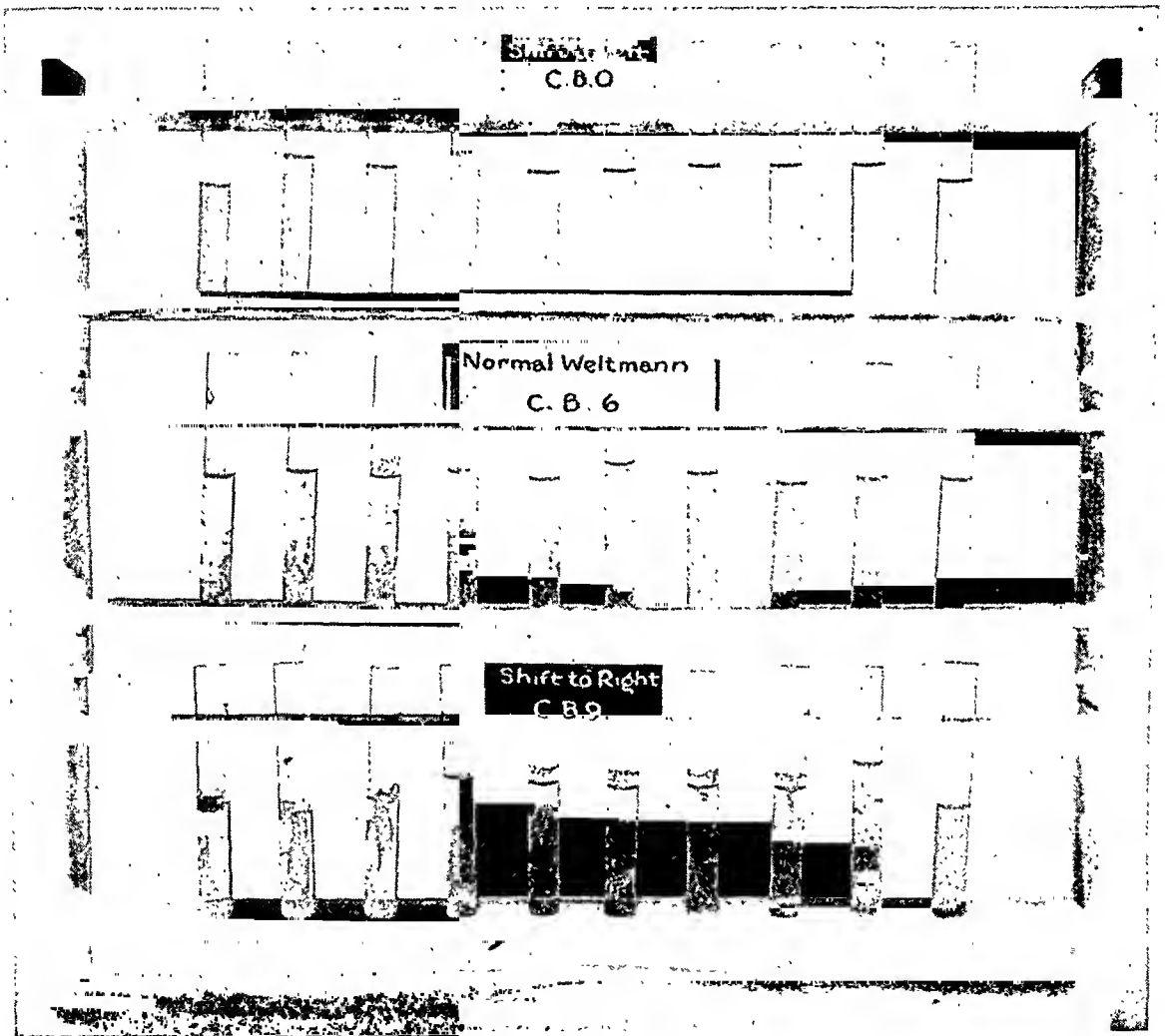


FIG. 1. A photograph illustrating the three different zones in the Weltmann reaction.<sup>5</sup>

The top row shows no coagulation in any of the tubes, indicating a marked shift to the left. The coagulation band is zero. This is from a patient with lobar pneumonia.

The middle row shows a normal Weltmann reaction with coagulation extending to the sixth tube and giving a coagulation band of 6.

The bottom row shows coagulation to the ninth tube, illustrating a marked shift to the right with a coagulation band of 9. This is from a patient with cirrhosis of the liver.

ditions like pneumonia and dysentery the concentrations of the blood varied greatly from day to day, being affected in a great measure by the intravenous administration of fluids, so that when the sedimentation rate was not corrected, erroneous results were obtained.

In figure 1 we reproduce an illustration which appeared in an earlier report of ours.<sup>5</sup> The ease with which the test can be read is apparent.

In figure 2 we have grouped according to the coagulation band a large

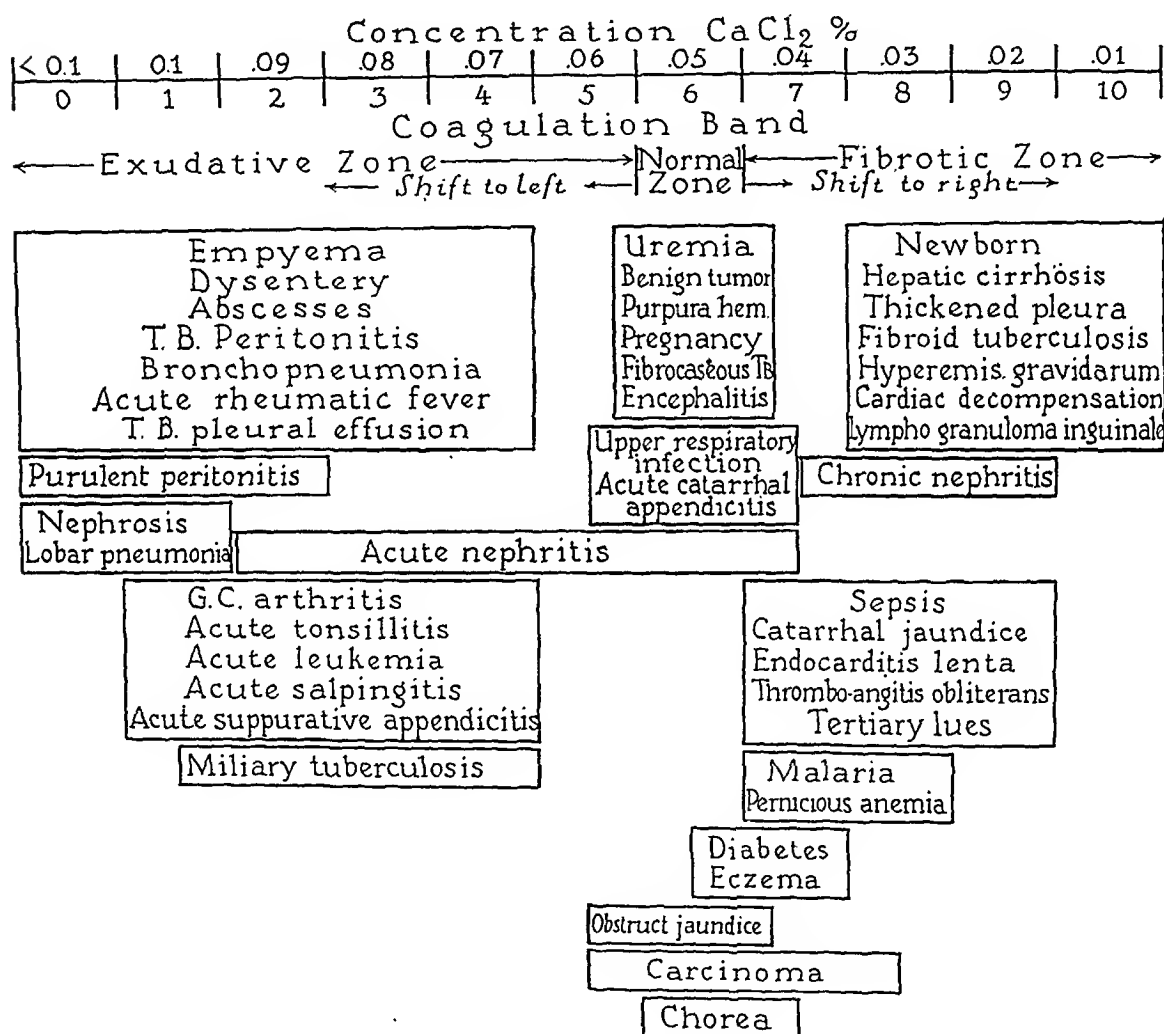


FIG. 2. A chart illustrating the three zones of the Weltmann reaction. The ranges of the coagulation band in some of the diseases studied are shown.

number of the conditions that were studied. A similar table on a much smaller scale was presented by Purper.<sup>6</sup> It is seen that the acute exudative diseases give a low coagulation band or shift to the left in the Weltmann reaction. The degree of the shift to the left is usually proportional to the magnitude of the exudative process. Lobar pneumonia and acute suppurative appendicitis, for example, give a greater shift to the left than bronchopneumonia or acute catarrhal appendicitis. Febrile conditions un-

associated with foci of inflammation, or in which the latter play a very minor rôle, usually give an increased coagulation band. Malaria, septicemia and endocarditis lenta are examples of this. Predominantly fibrotic conditions such as hepatic cirrhosis, fibrous tuberculosis, thrombo-angiitis obliterans and tertiary lues also give a shift to the right. The same is true for catarrhal jaundice, whereas obstructive jaundice usually gives a normal Weltmann reaction. Among the conditions which give a normal coagulation band are uremia, diabetes, pregnancy, encephalitis and tumors.

The only non-febrile, non-inflammatory condition which has, in our experience, given a marked shift to the left is the nephrotic syndrome. The coagulation band here is usually zero, even though the patient has lost his edema and is clinically improved. The shift to the left does not primarily depend upon the serum protein changes since it persists even when the blood chemistry approaches normal levels.

The Weltmann reaction is of practical value in the differential diagnosis of febrile disturbances because it establishes the nature of the pathological condition, that is, whether it is an exudative or a non-exudative or septic state. To illustrate, we present the following two case reports.

#### THE WELTMANN REACTION IN A PATIENT WITH TYPHOID FEVER

*Case 1.* L. C., a colored boy of 9, was admitted to the Cook County Hospital on July 18, 1936, with the complaints of abdominal pain for four days, and nausea, vomiting and fever for two days. He had been perfectly well up to July 15 when he began to have cramp-like pain in the abdomen, especially on the right side. Two days later he became nauseated and began to vomit everything he ate, and fever was noted for the first time. He felt better the following day, but that evening he began to cough, his abdomen seemed to be "swollen" and he was delirious. On admission to the hospital his temperature was 104° F., pulse 120, respirations 28. The abdomen was distended and moderately tender, especially in the right lower quadrant, but there was no definite rebound rigidity. Peristaltic sounds were slightly less than normal. There were a few coarse râles in both pulmonary bases but physical examination otherwise was negative. The white blood count was 12,000 with 70 per cent polymorphonuclear leukocytes. The provisional diagnosis was peritonitis due to a ruptured appendix or pneumonia. Careful examination the next day did not reveal evidence which would warrant a diagnosis of peritonitis, and the patient was transferred to the medical service.

On July 20 the Weltmann reaction gave a coagulation band of 6, which was interpreted as ruling out an acute exudative condition like pneumonia or purulent peritonitis, and being in favor of a septic infection or typhoid fever, and a blood culture was suggested. Roentgenogram of the chest made the following day showed no abnormality. The blood culture taken July 22 was positive for *B. typhosus* and on July 24 the same organism was isolated from the stool. Although he was quite toxic and his temperature remained about 105° F. for 10 days, the boy became afebrile after three weeks and made an uneventful recovery. The coagulation band was determined five times during the boy's illness and at no time was there a shift to the left.

#### THE WELTMANN REACTION IN A PATIENT WITH ENDOCARDITIS LENTA

*Case 2.* A. R., a white boy 6 years old, was admitted to the Cook County Hospital January 29, 1937 complaining of pains in the legs, which began two weeks

previously and lasted for about six days. He had been in bed since the onset, perspired easily, and seemed warm. Three days before admission he complained of pain in the right side of the abdomen, and he vomited four times. The day before entrance into the hospital he had a severe nosebleed. The past history and family history were negative except that one brother had rheumatic heart disease.

On admission the rectal temperature was 99° F., pulse 100 and respirations 24. Physical examination revealed a pale, under-developed boy of 6 who seemed alert and had no special complaints. There was dried blood in the right nostril, the tonsils were large, cryptic and slightly reddened, and there were several carious teeth. The left heart border was out to the anterior axillary line, and the right border 1 cm. beyond the right sternal margin. There was a long loud systolic murmur at the apex. The heart tones were loud and regular. The abdomen and extremities were negative.

The white blood count was 15,400 with 89 per cent polymorphonuclear leukocytes, and the red blood count was 3,250,000 with 46 per cent hemoglobin. The urine showed a trace of albumin. A two meter roentgenogram of the heart showed moderate cardiac enlargement of the mitral type. The electrocardiogram was essentially normal.

The provisional diagnosis was an acute exacerbation of chronic rheumatic carditis with mitral insufficiency. The following day the temperature rose to 102° F., the sedimentation rate was 30 mm. and the coagulation band 5. The patient continued to be febrile and two days later the coagulation band was again 5 and on February 10, eleven days after admission, it was 6. The normal coagulation band was at variance with our findings of a marked shift to the left in cases of active rheumatic carditis. Although there were no petechiae and the spleen at this time was not palpable, a diagnosis of subacute bacterial endocarditis was made. The next day the spleen became palpable and petechiae appeared a week later. Although early blood cultures were negative, in one obtained March 3 non-hemolytic streptococci were found and the formol gel test became positive. The septic course continued, and three blood transfusions were given, but the boy died 41 days after hospitalization. No autopsy was performed, although the diagnosis of subacute bacterial endocarditis was justified by the ultimate clinical course. In this case the Weltmann reaction spoke against acute rheumatic fever before the usual characteristics of subacute bacterial endocarditis appeared.

When considered with other laboratory findings the Weltmann reaction may help to make the diagnosis or may substantiate a diagnosis made previously. As more clinical conditions will be studied, the diagnostic possibilities of the test will doubtless be increased.

#### THE SEDIMENTATION RATE AS A DIAGNOSTIC AID

Of all non-specific laboratory tests, none has attracted more attention or been more widely acclaimed than the sedimentation rate of the erythrocytes. This test has been studied in practically all disease conditions, but its value is not agreed upon by various investigators. Inflammatory states and conditions associated with tissue destruction give a rapid sedimentation rate. A slow sedimentation rate has been characteristic only in allergic conditions and in the new born infant. The sedimentation rate has been of greatest value in detecting pathological conditions which are subclinical, and in following the progress of the individual in chronic conditions, especially tuberculosis and rheumatic fever. In the diagnosis of acute febrile

disturbances, the sedimentation rate is of little value since it is increased in almost all such conditions. Recently, however, it has been pointed out that in acute appendicitis the sedimentation rate is relatively normal, whereas in acute salpingitis it is increased.

#### COMPARISON OF THE WELTMANN REACTION WITH THE SEDIMENTATION RATE

We have compared the coagulation band with the corrected sedimentation rate in 121 unselected cases as shown in figure 3. Our findings agree with those of Carrière, Martin and Duffossé,<sup>7</sup> in that there is no definite correlation between the Weltmann reaction and the sedimentation rate. Although a low coagulation band is very frequently associated with a rapid sedimentation rate, a normal or increased coagulation band may also be found with a rapid sedimentation rate. In those conditions which give a normal or increased coagulation band the sedimentation rate may be normal or rapid. A coagulation band of 6 or more with a rapid sedimentation rate may be found in malaria, sepsis, lymphogranuloma inguinale, tertiary syphilis and in the convalescent or healing stages of tuberculosis and rheumatic carditis.

Although the mechanisms of both the Weltmann reaction and the sedimentation rate are not known, the former depends on fewer factors and is more stable. In normal pregnancy the sedimentation rate is increased but the coagulation band is normal. It has also been shown<sup>8</sup> that there is a normal diurnal variation in the sedimentation rate which may be of such magnitude that in the same patient at one time of the day a normal value may be obtained, and at another time a pathological sedimentation rate may be found. This is not true of the Weltmann reaction. Yardumian,<sup>9</sup> after studying the influence of various factors on the sedimentation rate in over 2,000 conditions, concludes that "it is inconceivable that a phenomenon so readily influenced by many variable factors should be of appreciable diagnostic and prognostic value."

We have compared the sedimentation rate and coagulation band with the progress of the clinical condition in a large number of cases of lobar pneumonia, tuberculosis and rheumatic fever. In uncomplicated lobar pneumonia, the coagulation band gives a shift to the left, and in our experience has always been zero at the time of consolidation. After the onset of clinical resolution, the coagulation band begins to increase but takes several days to two weeks to return to normal. In those cases having more than one lobe of a lung involved, the coagulation band returns to normal more slowly than in those with only one lobe, or a portion of a lobe consolidated. The sedimentation rate is usually rapid at the onset of the condition, and is frequently still faster than normal when the coagulation band has returned to 6. We have constructed sedimentation curves, reading the sedimentation at 15 minute intervals for 1½ hours in a number of cases of lobar pneumonia

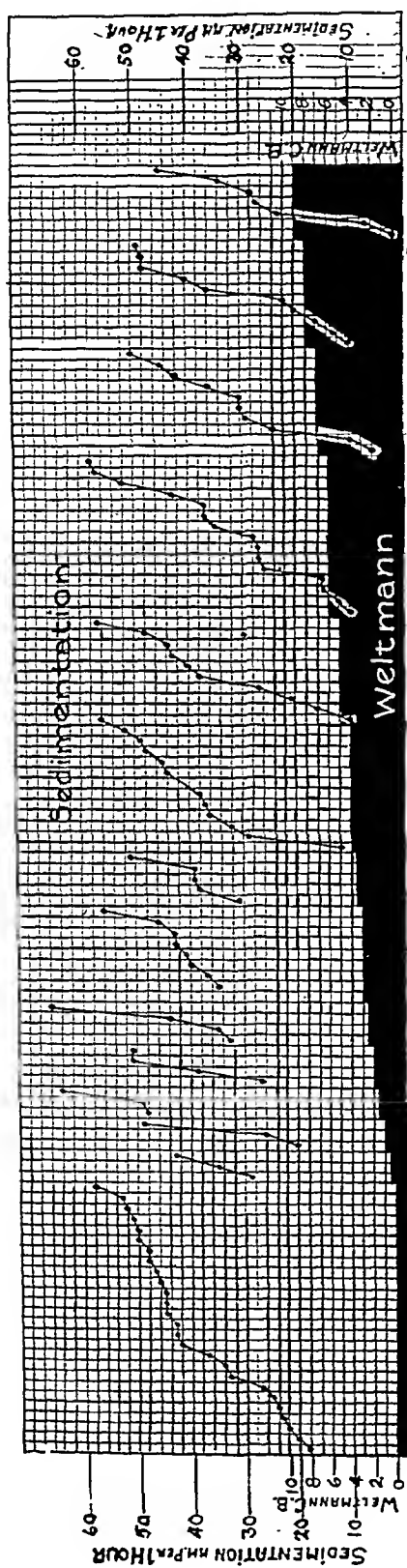


FIG. 3. A comparison between the coagulation band, indicated by the black area, and the corrected sedimentation rate, indicated by the connected dots. It is seen that a rapid sedimentation rate is found throughout the range of the coagulation band.

and cannot support the findings of Brooks<sup>10</sup> who stated that the sedimentation curves follow particular patterns according to the stage of the pneumonia. At the time of the crisis the sedimentation rate, in our hands, not infrequently becomes slower or even normal, and several days later returns to its former high level. Furthermore there is a great variation in the sedimentation rate from day to day irrespective of the clinical condition of the patient. This is especially true in children. We have illustrated these findings in the following figures.

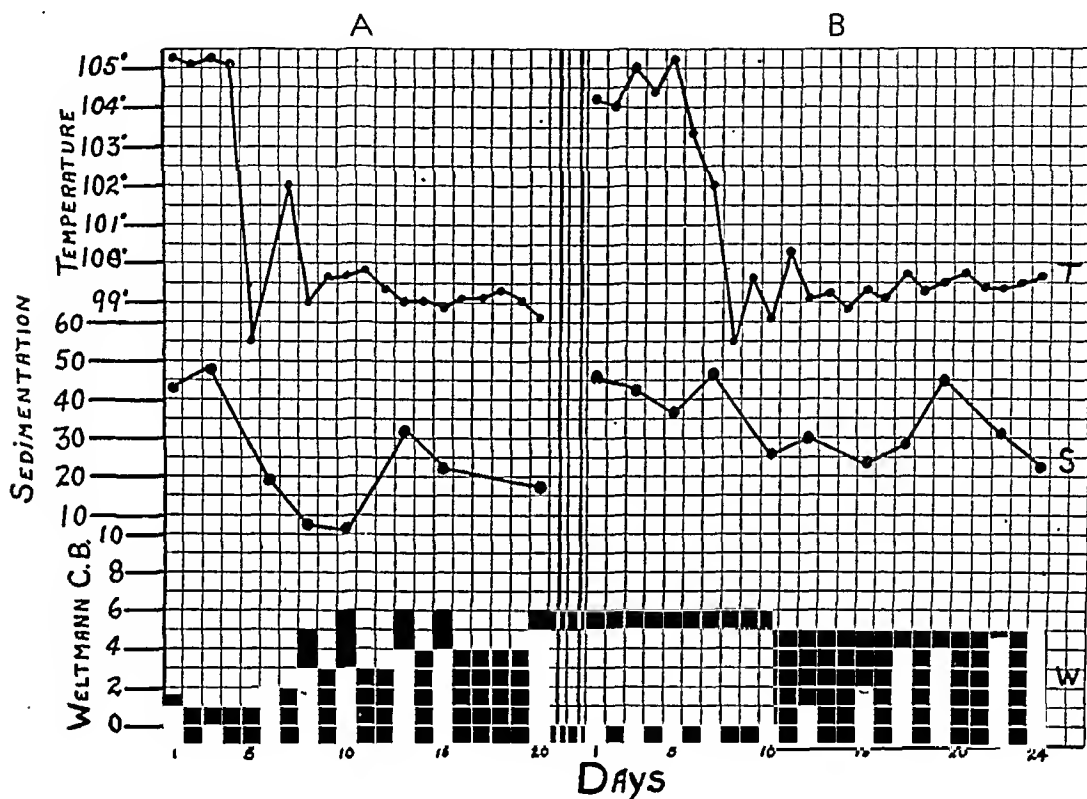


FIG. 4 A. Comparison of coagulation band, sedimentation rate and temperature in a case of lobar pneumonia with a consolidation of part of the right lower lobe.

B. Comparison of coagulation band, sedimentation rate and temperature in a case of lobar pneumonia with consolidation of the right middle and lower lobes.

#### DETAILED ANALYSIS OF PATIENTS WITH PNEUMONIA (FIGURE 4 A AND B)

C. R. (figure 4 A), a 6 year old Mexican boy, was admitted to the hospital December 28, 1936, with the complaints of cough for five days and pain in the chest, fever and rapid breathing for three days. On admission the temperature was 105.4° F., pulse 142 and respirations 40. There was clinical and fluoroscopic evidence of a pneumonia involving part of the right lower lobe. The white blood count was 20,000 with 86 per cent polymorphonuclear leukocytes. The clinical course was uneventful. There was a pseudo-crisis on the fourth hospital day (ninth day of illness) and the temperature was normal on the sixth day. On admission the coagulation band was 1½ and two days later it went down to zero. After resolution the coagula-

tion band returned rapidly to normal and reached 6 on the third afebrile day. The sedimentation rate was rapid at the beginning of observation, dropped to normal during the crisis and then rose again.

We compare this with another case of lobar pneumonia in which there was more extensive lung involvement.

L. A (figure 4 B), a white boy of 7, was admitted to the hospital with complaints of cough for two weeks and fever and vomiting for one day. On admission his temperature was 104.6° F., pulse 138 and respirations 42. There were signs of consolidation in the right middle and lower pulmonary lobes. The white blood count was 33,000 with 79 per cent polymorphonuclear leukocytes. The first coagulation band was determined on the sixth hospital day (seventh day of illness) and was zero. The sedimentation rate was 45 mm. in one hour. The boy was very toxic but had a crisis on the eighth day of observation or fifteenth day of illness and went home 16 days after the crisis. The coagulation band began to increase on the fourth afebrile day but was 5 (slightly to the left) on the sixteenth day when he went home. The sedimentation rate fluctuated considerably, showed a distinct drop after the crisis, and then rose to its former high level 11 days after the crisis.

#### DETAILED ANALYSIS OF PATIENT WITH EMPYEMA (FIGURE 5)

A. R., a boy of 13, was admitted to the hospital complaining of pain in the left chest, fever and severe abdominal pain for two days. The clinical findings were those of a left lower lobar pneumonia. Temperature was 102° F., pulse 120, respirations 26. The following day a roentgenogram showed a small amount of clouding in the lower left lung field. An empyema was detected on the fifth day and after the chest had been tapped several times, closed drainage was instituted on the eleventh day. The boy was very sick and toxic for two weeks, but he gradually improved and went home after having been in the hospital 77 days. At the time of discharge there was only slight drainage.

In figure 5 the Weltmann reaction is compared with the sedimentation rate and temperature. Throughout the 77 days the sedimentation rate remained rapid at about the same level, and thus did not at all reflect the clinical progress of the patient. The

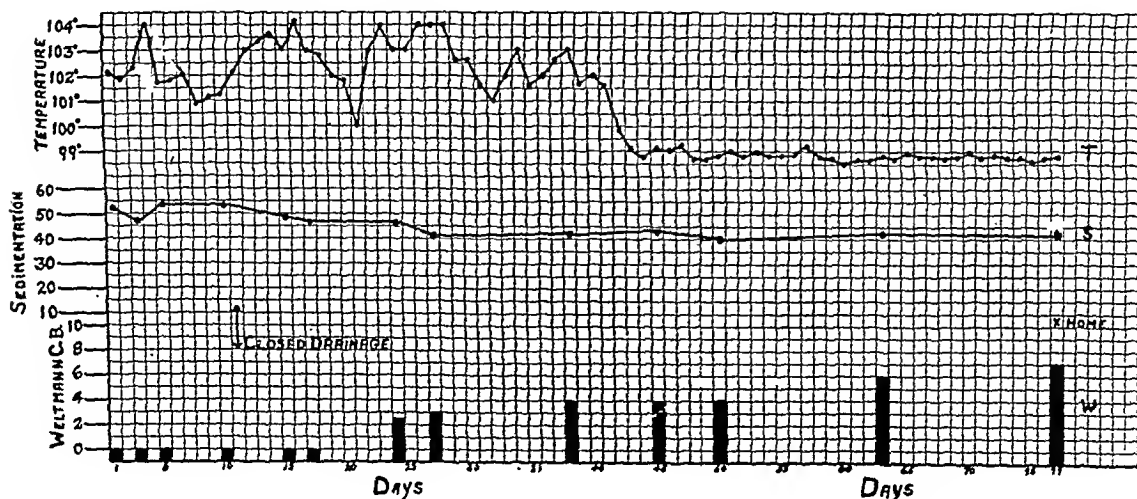


FIG. 5. Chart comparing the coagulation band, sedimentation rate, and temperature in a 13 year old boy with pneumonia and empyema.



coagulation band, however, was zero at the onset of observation and began to increase after adequate drainage was begun and became normal on the sixty-third day. In this case the coagulation band was a much better index of the clinical and pathological events than the sedimentation rate.

#### COMPARISON OF THE WELTMANN REACTION WITH THE SEDIMENTATION RATE IN ACUTE RHEUMATIC FEVER

Numerous investigators<sup>11</sup> have stressed the value of the sedimentation rate as a guide in determining activity of the rheumatic process. We have studied and compared the sedimentation rate and the coagulation band in more than 100 cases of acute rheumatic fever of childhood, and our observations on the sedimentation rate agree with the reports previously mentioned. Simple chorea unassociated with carditis gives a normal sedimentation rate, irrespective of the clinical severity of the condition. Acute rheumatic arthritis and carditis give rapid sedimentation rates. After the disappearance of the clinical signs and symptoms of infection, the sedimentation rate remains rapid for variable lengths of time. In monocyclic rheumatic arthritis, the average time required for the sedimentation rate to return to normal after the patient was free from fever was three weeks. In polycyclic rheumatic arthritis, the sedimentation rate remained faster than normal for two months, whereas in carditis it was often three to five months before the sedimentation rate became normal.

The coagulation band in chorea is usually normal, but in acute rheumatic arthritis and carditis there is a shift to the left which is in most cases proportional to the severity of the clinical condition. The sedimentation rate, however, is just as rapid in a mild case as in a severe case. As improvement occurs the coagulation band returns to normal before the sedimentation rate, and frequently even shows a shift to the right when the sedimentation rate is still rapid.

Although the sedimentation rate must still be regarded as the best available criterion as to when the patient with acute rheumatic fever may be allowed to resume a more active life, we do not believe that the rheumatic infection remains active in all cases as long as the sedimentation rate is rapid. When the clinical condition of the patient indicates subsidence of the infection and the coagulation band has returned to normal, the patient is convalescing even though the sedimentation rate may be as rapid as when there was fever, tachycardia and joint pains. The sedimentation rate cannot be used as an index of the onset of convalescence or repair because it frequently is just as rapid when fibrosis is taking place as when there is an acute inflammatory exudative process. We have shown this in an example of empyema (figure 5). When the sedimentation rate becomes normal and convalescence is over, the whole train of pathological events has come to a standstill and the patient is restored to normal. From this viewpoint the sedimentation rate is a better guide in determining when the rheumatic process is ended, but the coagulation band gives a truer insight into the actual pathological events taking place.

## DISCUSSION

Our results in the main agree with most of the published reports in the European literature on the Weltmann sero-coagulation band. The Weltmann reaction is a simple and easy test which distinguishes exudative from productive anatomic changes, and therefore becomes a valuable diagnostic criterion as well as a prognostic aid in various disease conditions. Examples of this we have presented in the text.

In view of the fact that this test is a nonspecific reaction and is not diagnostic of any disease, the clinician must interpret the Weltmann coagulation band as another biological reaction which the patient presents and evaluate it accordingly. When the laboratory worker examines the patient's serum he can only state that the reaction is in the normal zone, gives a shift to the left in the exudative zone or to the right in the fibrotic or septic zone. The clinician familiar with the patient's clinical history and physical findings can now interpret the Weltmann reaction in a fashion which will enable him to at once classify the patient's condition as one of exudative or fibrotic anatomic changes. For example, in pulmonary tuberculosis exudative changes result in a coagulation band to the left, whereas fibrotic changes give a coagulation band to the right.

When we apply the Weltmann reaction to a great variety of clinical conditions we obtain valuable assistance from this test particularly in relation to diagnosis. It is fairly well established that the normal coagulation band is in tube 6 to 6½, representing the concentration of  $\text{CaCl}_2$  in 0.05 per cent to 0.04 per cent. We shall now briefly indicate the diagnostic value of the Weltmann reaction in some of the more important diseases, and have arranged these for the sake of simplicity, according to systems.

## THE WELTMANN REACTION AS A DIAGNOSTIC AID IN SOME OF THE MORE IMPORTANT DISEASES

*Liver Diseases.* As a rule in diseases of the liver and gall-bladder, the coagulation band is shifted to the right, more markedly so if there is cirrhosis or a parenchymatous affection of the liver. In obstructive jaundice, due either to stone or neoplasm, the coagulation band is within normal limits. In hepatic diseases associated with jaundice or ascites, the coagulation band is not materially affected as far as a swing to the right is concerned. Thus, in catarrhal jaundice when there is a disturbance in the parenchyma of the liver, the coagulation band extends to tubes 7 and 8; and when there is atrophy of the liver as in cirrhosis of the liver, the coagulation band extends to the ninth or the tenth tube.

We had an opportunity to examine the Weltmann reaction in salvarsan icterus and we have observed that the coagulation band usually reaches the eighth or ninth tube. Weltmann and Sieder<sup>12</sup> have pointed out that icterus due to antimony gave a similar result.

*Infections.* In various septic conditions and frequently in typhoid fever, the coagulation band reaches tubes 6 to 8. It is this important manifestation that differentiates sepsis from pneumonia, abscess, gangrene and other exudative lesions. Purper<sup>13</sup> has also indicated that the Weltmann reaction can be used as a differential diagnostic test in separating sepsis from the various forms of exudative changes. In most cases of typhoid fever we have obtained a normal coagulation band in the different weeks of the disease. Kretz and Kudlac<sup>14</sup> and Scherleitner<sup>15</sup> have obtained a shortened coagulation band in the first week of typhoid fever, but as a rule the Weltmann reaction in our cases was within normal limits. This reaction is altered when complications such as pneumonia, perforation and peritonitis occur, and then the coagulation band swings toward the left.

In scarlet fever, particularly in the first week of the disease, the coagulation band may vary anywhere from zero to tube 4, although Kretz and Kudlac<sup>14</sup> in their series of scarlet fever patients examined between the first and sixth week of the disease reported a normal coagulation band.

*Cardiovascular Diseases.* Non-infective heart disease gives a normal coagulation band. This is true particularly if the cardiac condition is compensated. Should the disease process progress toward decompensation, then there is a tendency for the Weltmann reaction to shift toward the right, which reflects a parenchymal damage to the liver. Similar observations in heart disease were shown by Kisch.<sup>16</sup>

In acute rheumatic carditis the coagulation band ranges from zero to tube 5, and in subacute bacterial endocarditis from tube 5 to tube 9. This suggests the possibility of the Weltmann reaction as a diagnostic criterion in distinguishing these two types of heart disease.

*Vascular Diseases.* Thrombosis and occlusion of the blood vessels usually were accompanied by a normal coagulation band or a slight shift to the right. If this condition was associated with destructive changes in the surrounding tissues, or if the disease was accompanied by a cellulitis or a lymphadenitis, the coagulation band gave a marked shift to the left and at times reached the first tube.

*Blood Dyscrasias.* The acute leukemias gave a shift to the left whereas the chronic leukemias usually gave a normal or increased coagulation band. In those diseases of the blood associated with fibrosis of the spleen such as Hodgkin's disease, Cooley's anemia, Banti's disease and sickle cell anemia, the coagulation band was also increased, whereas in the simple secondary anemias and in purpura hemorrhagica it was normal.

*Bone.* In arthritis, the Weltmann reaction was within the normal zone or gave a slight shift to the right. Hennes and Kemen<sup>17</sup> observed 38 cases of primary chronic polyarthritis of which 26 were proliferative and 12 exudative in nature. The authors compared the coagulation band with the sedimentation rate and pointed out that there was no correlation between these two tests.

In acute rheumatic arthritis, osteomyelitis and gonococcal arthritis, the

coagulation band was usually shortened in proportion to the severity of the condition. In chronic arthritis and quiescent gonorrheal arthritis the Weltmann reaction was within the normal zone. In early cases of gout the coagulation band was in tube 1. In acute osteo-arthritis of the ankles, hips and spine, the coagulation band gave a distinct shift to the left. In septic arthritis the Weltmann reaction was more nearly normal even though the joint was severely involved. The septic state usually overshadows the exudative process and draws the coagulation band toward the normal.

*Pregnancy.* The Weltmann reaction is within normal limits in pregnancy, but fetal blood as a rule gave a prolonged coagulation band which may be due to the physiological insufficiency of the liver in the new born. In the toxemias of pregnancy, the coagulation band showed a shift to the left.

In *gynecological conditions* particularly when the Fallopian tubes show inflammatory changes, the coagulation band is of great assistance in diagnosis. Here the coagulation band gives a shift to the left to tube 2, and in subacute salpingitis the coagulation band swings toward the right to tubes 4 and 5. As the pathological condition becomes quiescent the Weltmann reaction is normal or slightly to the right. In incomplete abortion, the coagulation band may vary from tube 3 to tube 6. In all benign tumors of the uterus the Weltmann reaction was normal or slightly to the right.

*Gastrointestinal Diseases.* Benign processes such as ulcers of the stomach or duodenum, during the quiescent stage, give a normal coagulation band. When complications such as perforation occur, the Weltmann reaction immediately shifts to the left. This also holds true when bleeding occurs in cases of peptic or duodenal ulcer. Terminal ileitis gives a Weltmann reaction in tube 6.

*Appendicitis.* The Weltmann reaction is of marked assistance in the diagnosis of exudative involvement of the appendix. We have had occasion to determine the coagulation band before operation in many patients in whom a clinical diagnosis of acute or chronic appendicitis had been made. Invariably if the coagulation band gave a shift to the left, the gross as well as the histological examination of the appendix removed revealed either acute suppuration, gangrene, or peri-appendiceal abscess. In chronic appendicitis, fecoliths of the appendix, in fibrous obliterative appendicitis and in acute catarrhal appendicitis the coagulation band was normal.

*Kidneys.* Most renal conditions are secondary to or associated with pathological conditions elsewhere in the body so that there is a wide variation in the coagulation band. Acute nephritis may give a shift to the left, a normal coagulation band or even a slight shift to the right. In post-scarlatinal nephritis the coagulation band may be wider than in nephritis associated more directly with foci of inflammation such as tonsillitis or cervical adenitis. Chronic nephritis gives a marked shift to the right, but in the nephrotic syndrome the coagulation band is very low, being zero in most

cases. Pyelitis gives a variable reaction similar to that found in acute nephritis, but perinephritic abscess gives a constant shift to the left. In cases of uremia without inflammatory complications the coagulation band is usually normal. The same is true for hydronephrosis.

*Skin.* In lymphogranuloma inguinale the coagulation band varies according to the condition of the lesions. When there is much tissue destruction the coagulation band is narrow, and when fibrosis is the predominant process it is far to the right, being often 9 or 10. The sedimentation rate is usually rapid irrespective of the coagulation band. Chancroids and chancres give a normal reaction, or one slightly below normal in tube 5. Secondary or tertiary syphilis usually will cause the coagulation band to deviate toward the right. This apparently reflects productive changes which are the rule in syphilis, and is in contrast with exudative changes which may occur in tuberculosis. It is of interest to note here that the shift to the right in syphilis is independent of the positive or negative Wassermann reaction.

*Diabetes.* In our series of patients who had diabetes mellitus the coagulation band was normal or slightly above normal. When complications occur such as gangrene or vascular occlusion, the coagulation band may drop to normal or slightly below normal.

*Tumors.* In benign tumors of all types the Weltmann reaction invariably was within the normal zone. In carcinoma, as a rule, the Weltmann reaction gave a slight shift to the left, and as the carcinoma underwent degenerative changes to the stage of necrosis and abscess formation, the Weltmann reaction gave a shift to the left, and at times to the zero or first tube. When metastases occurred the Weltmann reaction shifted to the left.

*Miscellaneous.* Froelich's syndrome gives a coagulation band in tube 8. In myxedema, the coagulation band was 5; and in Paget's disease the coagulation band was in tube 8. In hemorrhage and trauma of the brain which did not result in an immediate death the Weltmann reaction, as a rule, was either normal or slightly below normal in tube 5. In purulent infections of the brain and all suppurative forms of meningitis the Weltmann reaction was invariably in tube zero. In encephalitis and in lead encephalopathy the coagulation band was usually normal. Tuberculous meningitis gives a moderate shift to the left. In hypo- and hyperthyroidism the coagulation band was in tubes 5 to 7.

Spinal fluid invariably gives a negative reaction in tube zero, obviously due to the extremely low total protein. We have had occasion to examine blood and ascitic fluid from a patient with cirrhosis of the liver. The coagulation band in ascitic fluid was in one tube less than the coagulation band of the blood. For example, when the coagulation band was in tube 7 the ascitic fluid was in tube 6, and when the coagulation band of the blood was in tube 6 the ascitic fluid was in tube 5.

## THE WELTMANN REACTION AS AN AID IN PROGNOSIS

From the standpoint of prognosis the Weltmann sero-coagulation band is extremely helpful. This is particularly true when the Weltmann reaction is repeated frequently in the same patient. This test reflects anatomic alterations so that when the coagulation band shifts to the left it manifests exudative changes, and as it swings toward the right it indicates fibrotic processes. This reaction suggests that the clinical condition is either becoming unfavorable and that complications have developed as is manifested by the coagulation band in the exudative zone, or that the pathological condition is becoming arrested and that the patient is improving as indicated by a return to normal or to the fibrotic zone. The sedimentation reaction has been used extensively in prognosis as well as an aid in the differential diagnosis of various clinical conditions. We have compared this test with the Weltmann reaction and have found that the coagulation band does not at all times agree with the sedimentation reaction. In fact the sedimentation reaction has at times been misleading in interpreting the patient's clinical progress. For example, in both rheumatic carditis and endocarditis lenta, the sedimentation reaction is rapid although in the former condition the underlying anatomic change is exudative, and in the latter septic. The Weltmann reaction here is of more assistance, since in rheumatic carditis it gives a shift to the left and approaches normal as the process becomes arrested; whereas, in endocarditis lenta, the coagulation band is normal or to the right. Another example of the divergence of interpretation between the sedimentation and the Weltmann reactions is that of sepsis. In this condition the Weltmann reaction gives a normal coagulation band or a shift to the right whereas the sedimentation reaction is rapid. The coagulation band may also be used in prognosis as a quantitative index of tissue destruction and repair, as is seen in tuberculosis.

## MECHANISM OF THE WELTMANN REACTION

As to the mechanism of the Weltmann reaction very little is known. Nannini and Marani<sup>18</sup> believed that an increase in the globulin and a decrease in the albumin is necessary for a shortening of the coagulation band. In contrast to this Carrière, Martin and Duffossé<sup>7</sup> could find no relation between the coagulation band and the albumin-globulin ratio.

In 75 patients the Weltmann reaction was compared with the total serum protein, albumin, globulin and the albumin-globulin ratio.

Table 1a illustrates the total serum protein values as compared with the coagulation band. It is seen that where the total serum protein is less than 7 mg. per cent the coagulation band may extend throughout the range from 0 to 9. Where the total serum protein is more than 7 mg. per cent the coagulation band is rarely less than normal. Table 1b compares the albumin-globulin ratio with the coagulation band. Where the albumin-globulin ratio is less than 1.5 the Weltmann reaction may be normal or give

TABLE IA  
Relation of Total Serum Protein to Coagulation Band

No. Cases	Total Protein	Range of Coagulation Band											
			0	1	2	3	4	5	6	7	8	9	10
22	-5 mg.	Case Distrib.	5	2	3	1	2	5	2	1	0	1	0
41	5-7 mg.		1	2	3	3	3	7	13	3	6	1	0
12	+7 mg.		0	0	0	0	2	0	5	1	2	2	0

TABLE IB  
Relation of A/G Ratio to Coagulation Band

No. Cases	A/G Ratio	Range of Coagulation Band											
			0	1	2	3	4	5	6	7	8	9	10
27	-1	Case Distrib. "	3	2	3	0	2	4	3	2	6	2	0
30	1-1.5		3	2	1	4	4	5	5	3	2	1	0
13	1.5-2.0		0	0	0	0	0	2	7	3	1	0	0
5	+2.0		0	0	1	0	1	0	2	0	0	1	0

either a shift to the left or right. Where the albumin-globulin ratio is more than 1.5 the coagulation band is more apt to be normal or greater than normal. We may conclude that the coagulation band gives no index as to the total serum protein or the albumin-globulin ratio. That the albumin-globulin ratio by itself is of little importance is further seen in table 2. In the nephrotic syndrome the total serum protein and the albumin are low, the globulin is normal or slightly increased, and there is an inverted albumin-globulin ratio. In this condition the coagulation band is to the left in the

TABLE II

	Total proteins	Albumin	Globulin	Albumin-globulin ratio	Weltmann
Nephrotic syndrome.....	3.58	1.33	2.25	0.59	0
Nephrotic syndrome.....	4.50	1.50	3.00	0.50	1
Cirrhosis of liver with ascites..	4.10	1.10	3.00	0.36	7
Cirrhosis of liver with ascites..	4.90	1.50	3.40	0.44	7

exudative zone in tube zero or tube 1. This is contrasted with an example of cirrhosis of the liver with ascites in which the quantitative protein picture of the serum is identical with that of nephrosis but here a normal or increased coagulation band is obtained in tube 7.

Goettsch and Reeves<sup>19</sup> believe that the serum proteins in nephrosis differ immunologically from normal serum proteins and this change may therefore be a significant factor.

Other suggestions as to the probable mechanism of the Weltmann reaction have been made by several investigators, but no definite proof has been given. Kretz and Kudlac<sup>14</sup> found that the chloride and calcium content of the serum have no effect on the coagulation band. They believe that the reaction depends upon a qualitative change in the serum protein. Weltmann found that the addition of bile does not alter the reaction. Hemolysis will cause an increased coagulation band.

The chemistry of the changes occurring in heat coagulation of protein are not completely understood, but several factors play a rôle. The most important appear to be the nature and amount of the protein itself, the pH, and the electrolytic content of the surrounding medium. Each protein itself may have its optimum pH and electrolytic threshold. Just what rôle is played by the electrolyte is difficult to estimate. We have determined the pH of the various dilutions of  $\text{CaCl}_2$  used in the reaction and found that the range of the pH was between 7.5 and 7.73 and it had no appreciable effect on the coagulation band. However, we have correlated the blood pH with the coagulation band and found that at times when there was a decrease of the pH of the serum there was a tendency for the coagulation band to become increased, and conversely, when the pH of the serum approached the alkaline side the coagulation band was decreased. This became more prominent when the blood pH was repeated often on the same patient, and we reported this in a previous publication.<sup>20</sup> We do not believe, however, that there is any essential relationship between the pH and the coagulation band. Both may be manifestations of the same underlying process. Some investigators as di Benedetto and Stornello<sup>21</sup> have pointed out that the reticulo-endothelial system is concerned with the management of the physical chemical equilibrium of the blood serum, which in different degrees of intensity may be common to several diseases.

We have performed in vitro absorption experiments using the method of Hektoen and Welker<sup>22</sup> in an attempt to obtain, if possible, some information as to the specificity of the negative phase in precipitin production.\* Under the conditions of our experiment the serum obtained from a patient showing a coagulation band in tube zero, did not appear to contain antigenic protein material which was not also present in normal serum showing a coagulation band in tube 6. In other words the precipitin reaction of the blood from a patient with a zero coagulation band, one from a normal coagulation band, and one with a coagulation band in tube 9, all gave precipitin reactions within the normal range.

### CONCLUSIONS

The Weltmann serum coagulation reaction is a simple test, easy to perform, and can be read within 15 to 20 minutes. It can be performed in a hospital laboratory as well as in a doctor's office. The test is not diagnostic

\* The immuno-chemical experiments were performed by Dr. C. A. Johnson of the Department of Physiological Chemistry of the University of Illinois College of Medicine.



for any disease, but is a nonspecific reaction which aids in distinguishing exudative from fibrotic processes. The normal coagulation band is between tubes 6 and 6½. When the coagulation band is limited to the first five tubes or less it indicates a shift to the left or an exudative reaction. When the coagulation band extends to more than six tubes, there is a shift to the right which indicates fibrotic changes. In general, acute inflammatory and exudative conditions cause a shortened coagulation band, whereas in chronic diseases characterized by predominating fibrotic processes, in healing stages of acute infections, in sepsis, and in parenchymatous liver damage, the coagulation band tends to be lengthened.

The coagulation band does not always agree with the sedimentation rate and reflects more accurately the pathologic-anatomic changes.

Although the mechanism of the serum coagulation reaction is not known, we believe that the Weltmann test may be a diagnostic as well as a prognostic aid in certain disease conditions, and has been shown to be of especial value in tuberculosis and rheumatic fever, and in distinguishing septic from non-septic febrile states.

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# PATHOLOGIC FINDINGS IN THE HEART IN SUDDEN CARDIAC DEATHS \*

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THIS communication is the report of a study of 41 hearts obtained from subjects who died suddenly from cardiac disease. One was from private practice † and 40 occurred at the New York City Hospital between January 1, 1927 and July 1, 1936.

During that period there were 82 cases of sudden death in the hospital that came to autopsy. Twenty-two were proved to be due to non-cardiac factors such as ruptured aneurysm, brain tumors, massive hemorrhage, etc. Of the remaining 60 cases 20 had to be discarded because of unsatisfactory histologic material.

For the purpose of this study cases were considered as sudden death when death was instantaneous or occurred within a few minutes after collapse. In none was it delayed more than 20 minutes and usually the time limit was less than ten.

Our findings proved to be different from the commonly accepted beliefs of the present day. We found the chief etiologic factor producing cardiac changes in these cases was infection, whereas arteriosclerosis occurred as a main factor in a comparatively small number.

## HISTOPATHOLOGIC CHANGES

The cases were classified for a working basis according to the main clinical or pathological diagnoses. The following table (1) gives the classification:

TABLE I.

Acute coronary thrombosis.....	10
Acute endocarditis.....	5
Acute coronary insufficiency.....	5
Deaths in infancy and childhood.....	5
Rheumatic heart disease.....	4
Syphilis and essential hypertension.....	4
Acquired syphilis.....	2
Syphilis and rheumatic heart disease.....	2
Acute pneumonia.....	2
Unexplained deaths.....	2
Total.....	41

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† Thanks are due to Dr. George R. Irving, New York City, for permission to include this case.

The one common pathologic finding in the entire series, with the exception of the two deaths that were unexplainable, was a damage to the myocardial fibers. It varied in degree and extent in different instances. It was mildest in the cases with interstitial polynuclear reaction, such as was present in the acute pneumonias of the adult, in which there appeared a molecular degeneration of the cytoplasm and a disturbance of the finer architectural pattern of the fiber. It was most severe in instances of acute coronary thrombosis in which the myomalacia was visible to the naked eye. It was of interest to note that in the latter group histological changes of mild degree were found well beyond the region of infarction and frequently in the muscle supplied by vessels free of thrombi.

The etiology of the myocardial damage varied somewhat but the most striking finding was the rôle played by infection. In 14 cases of the entire series there was an infectious process directly affecting the heart. These consisted of four cases of acute rheumatic myocarditis, five cases of acute endocarditis, two cases of acquired syphilis, two cases of combined syphilis and hypertension with a superimposed acute infectious endocarditis and one case of acute coronary insufficiency with bacterial arteriolar thrombi. In several instances more than one infectious factor was present in the same heart. The findings in this group of infectious myocarditides are summarized in table 2.

The cardiac damage in 12 other cases seemed toxic rather than infectious in nature. In these there was acute infection in other organs but no demonstrable bacteria in the heart. In eight of this group the myocardial damage was characterized by marked molecular degeneration associated with polynuclear reaction. Of this group the two cases of acute pneumonia in adults are examples. This is not unusual as toxic changes of the myocardium are a well known accompaniment of pneumonia. The changes in these two instances seem to have progressed a step further, sufficient to initiate a cellular response. In one case definite infection of the heart may have been present since the pneumonia was complicated by mediastinitis and fibrinous pericarditis.

The two cases of rheumatic heart disease and syphilis also had acute pneumonia and cardiac lesions similar to those in the two cases just mentioned in the preceding paragraph. In one of these there may have been definite infection in addition to the acute toxic degeneration since there was a fibrinous pericarditis and peritonitis present.

One case of acute coronary insufficiency was similar. That the bronchopneumonia in this instance was not simply that seen so frequently as a terminal event in coronary arteriosclerosis is indicated by the clinical history. He had been compensated and ambulant under maintenance doses of digitalis for five months and was found dead in bed.

Three of the cases in infancy and childhood were of the same type. The clinical features of these cases had several points of interest. Two children were apparently convalescing from acute upper respiratory infections with

TABLE II  
Infectious Myocarditides

Serial No.	Race	Sex	Age	Group	Under Observation	Anatomical Diagnoses	Remarks
1	W.	M.	18	R.H.D.	32 m	Chronic active rheumatic pancarditis. Acute rheumatic myocarditis. Acute bronchopneumonia. Acute fibrinous pericarditis.	Active rheumatic of moderate severity.
2	B.	M.	35	R.H.D.	4½ m	Chronic active rheumatic pancarditis. Acute rheumatic myocarditis.	Severe rheumatic without edema.
3	B.	F.	62	R.H.D.	1 m	Chronic active rheumatic valvulitis of mitral valve. Acute rheumatic myocarditis. Acute endocarditis of mitral valve. Acute myocardial abscesses.	Sarcoma uteri. Hysterectomy. Postoperative anginal attacks. Wound infection; streptococci in section.
4	W.	M.	41	R.H.D.	2 d	Healed rheumatic mitral valvulitis. Chronic active rheumatic valvulitis of tricuspid valve. Acute rheumatic myocarditis. Acute bronchopneumonia.	Paroxysmal dyspnea and cyanosis.
5	W.	M.	49	Acute endocard.	25 d	Chronic active rheumatic valvulitis of mitral aortic and pulmonic valves. Acute endocarditis of aortic valve. Acute myocardial abscesses. Acute splenic infarctions. Acute interstitial nephritis.	Slowly progressive congestive failure. Infected varicose ulcer of leg. No blood culture. Gram positive cocci in section of valve.
6	W.	M.	69	Acute endocard.	9 d	Healed rheumatic pancarditis. Acute endocarditis of mitral valve. Acute mural endocarditis of both ventricles. Acute arteriolar thrombi of LV and IVW. Acute military infarctions of heart.	Slowly progressive congestive failure. Joint pains. No blood culture.

TABLE II—Continued

Serial No.	Race	Sex	Age	Group	Under Observation	Anatomical Diagnoses	Remarks
7	W.	F.	28	Acute endocard.	20 d	Chronic active rheumatic valvulitis of mitral aortic and tricuspid valves. Acute gonococcal endocarditis of mitral and aortic valves. Acute gonococcal myocarditis. Emboli of spleen, kidneys and popliteal artery.	Clinically subacute bacterial endocarditis of 5 mos. duration. Positive blood cultures. Gonococci demonstrable in valves, myocardium and popliteal embolus.
8	B.	F.	21	Acute endocard.	23 d	Acute neisserian endocarditis of aortic valve with perforation through base of aorta into right auricle. Acute myocarditis.	3 wks. migrating arthritis following acute sore throat. Negative blood cultures. Organisms (meningococci?) in valve.
9	W.	M.	38	Acute endocard.	5 d	Acute staphylococcus endocarditis of tricuspid valve. Acute staphylococcus myocarditis. Acute staphylococcus abscess of prostate. Acute suppurative nephritis. Acute suppurative pericholecystitis. Chronic gonococcal prostatitis.	Urinary retention and instrumentation 1 mo. previously. Positive blood cultures <i>Staph. aur. hemo.</i> Staph. demonstrable in valve, myocardium and prostate; gonococci in prostate.
10	B.	M.	43	Acquired syphilis	11 m	Syphilis of aorta with incompetent valve and atresia of coronary mouths. Syphilitic myocarditis. Acute rheumatic myocarditis. Chronic pulmonary tuberculosis.	Ambulatory.
11	B.	F.	46	Acquired syphilis	20 d	Syphilis of aorta with incompetent valve and atresia of coronary mouths. Syphilitic myocarditis. Acute myocarditis (syphilitic?).	Decompensated.

TABLE II—Continued

Serial No.	Race	Sex	Age	Group	Under Observation	Anatomical Diagnoses	Remarks
15	B.	M.	42	Combined syphilis and hypertension	2 m	Commissural syphilis. Acute endocarditis of aortic valve. Syphilitic arteritis of intrinsic coronary arteries. Acute bronchopneumonia. Urethral strictures. Chronic pyelonephritis.	Congestive failure.
17	W.	M.	45	Combined syphilis and hypertension	3 m 1 m	Syphilis of aorta with incompetent valve. Acute endocarditis of aortic and mitral valves. Acute myocarditis. Arteriolar sclerosis of heart. Acute and subacute myocardial necroses. Acute bronchopneumonia. Chronic purulent bronchiectasis. Acute glomerulitis.	Clinically improving.
30	W.	M.	75	Acute coronary insufficiency	46 m	Acute miliary infarctions of heart. Bacterial arteriolar emboli of heart. Acute infarctions of kidneys. Chronic purulent bronchiectasis.	Partially decompensated.



FIG. 1. (Case 8.) Aortic valve in unidentified Neisserian endocarditis. The posterior leaflet is almost completely destroyed. The small diamond shaped defect toward the left in the sinus forms the base of a fungating mass presenting in the right auricle. The larger defect on the right is a deep ulcer filled with blood. The lesion of the leaflet is similar in Case 7.



a normal temperature for several days and evidence of gaining weight. The third child had apparently never been ill. He had been playing happily in his crib 15 minutes before being found dead. Another member of the family, however, had been confined to the home with acute sore throat, but was in isolation and had not been in contact with the child.

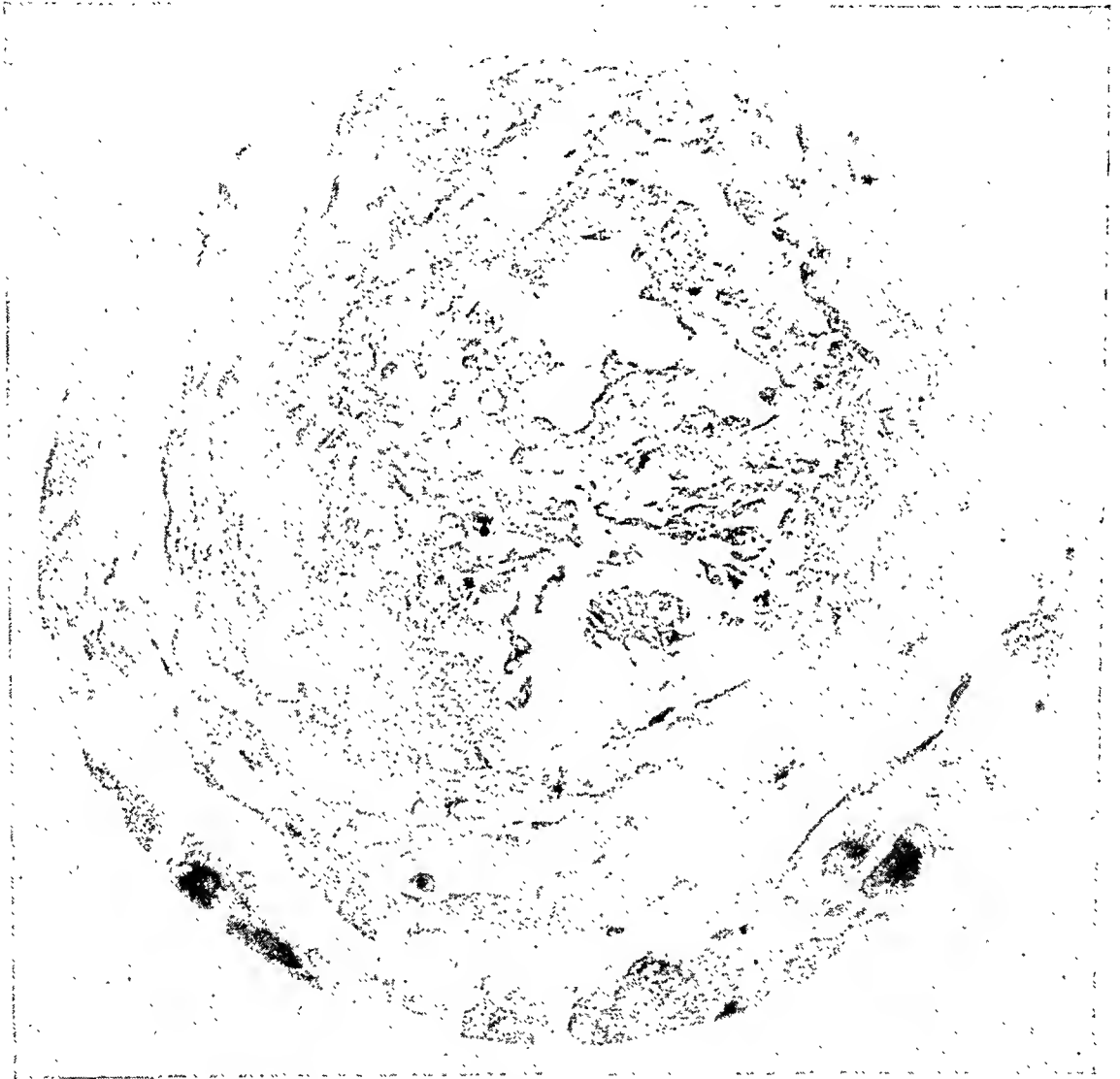


FIG. 2. (Case 15.) Syphilitic endarteritis of intrinsic coronary arteries in a case of combined syphilis and essential hypertension.

Two cases had acute coronary thrombosis of the superficial arteries and acute bronchopneumonia. One was in congestive failure. The other had suffered a first attack of angina a few days previously and clinically was improving rapidly. In this case the first attack had occurred a few days after a common head cold. The kidneys in both cases had focal glomerular lesions suggesting infection. Purulent masses were present in one, acute intracapillary hyaline thrombi in the other. In addition to the acute process,

TABLE III  
Toxic Myocarditides

Serial No.	Race	Sex	Age	Group	Under Observation	Anatomical Diagnoses	Remarks
12	B.	M.	26	Combined syphilis and rheumatism	5 w	Chronic active rheumatic pancarditis. Acute rheumatic myocarditis (limited). Acute interstitial myocarditis. Acute fibrinous pericarditis. Syphilis of aorta with incompetent valve. Acute lobar pneumonia. Acute fibrinous peritonitis.	Congestive failure.
13	B.	M.	34	Combined syphilis and rheumatism	8 w 6½ m 9 d	Chronic active rheumatic valvulitis of mitral aortic and tricuspid valves. Acute rheumatic myocarditis (limited). Acute interstitial myocarditis. Commissural syphilis of aorta. Acute bronchopneumonia.	Decompensated; anginal attacks.
23	W.	M.	66	Acute coronary thrombosis	2 m	Recent coronary thrombosis. Chronic purulent bronchiectasis. Acute bronchopneumonia. Acute glomerulitis.	Decompensated.
26	W.	M.	59	Acute coronary thrombosis	2 d	Recent coronary thrombosis. Chronic purulent bronchiectasis. Acute bronchopneumonia. Acute glomerulitis.	Clinically improving.
28	B.	M.	60	Acute coronary insufficiency	6 m	Acute myocardial necrosis. Acute bronchopneumonia. Chronic purulent bronchiectasis.	Compensated 5 mos.

TABLE III—Continued

Serial No.	Race	Sex	Age	Group	Under Observation	Anatomical Diagnoses	Remarks
31	W.	M.	67	Acute coronary insufficiency	2 w	Acute medial necrosis of coronary artery. Acute myocardial necrosis. Chronic purulent bronchiectasis.	Very slight decompensation.
32	W.	M.	50	Acute coronary insufficiency	3 w	Acute medial necroses of coronary arteries. Acute myocardial necrosis. Chronic purulent bronchiectasis.	Compensated with limited reserve for 3 wks.
33	B.	M.	33	Acute pneumonia	5 d	Acute interstitial myocarditis. Acute lobar pneumonia. Acute mediastinitis. Acute fibrinous pericarditis. Sickle cell anemia.	
34	W.	F.	67	Acute pneumonia	1 d	Acute myocarditis. Acute bronchopneumonia.	
35	B.	F.	3 m	Infancy and childhood	23 d	Acute myocarditis. Acute bronchopneumonia.	Acute upper respiratory infection. Gastroenteritis. Recovery. Clinically well for 1 wk.
38	B.	F.	45 d	Infancy and childhood	45 d	Acute myocarditis. Acute streptococcal pneumonia. Acute streptococcal sinusitis.	Acute upper respiratory infection. Recovery. Clinically well for 1 wk. <i>Strept. viridans</i> in cultures of lungs and sinuses at autopsy.
39	W.	M.	4½ m	Infancy and childhood	—	Acute myocarditis. Acute streptococcal pneumonia. Status lymphaticus.	Never ill; found dead in crib. <i>Strept. viridans</i> in cultures of nasal discharge and lungs at autopsy.

the lungs were the seat of an intense chronic purulent bronchiolitis with tubular bronchiectasis.

Two cases of coronary insufficiency with grossly normal vessels had acute medial necrosis of the superficial coronary arteries. The lesion resembled that described in the aorta which leads to 'spontaneous rupture.

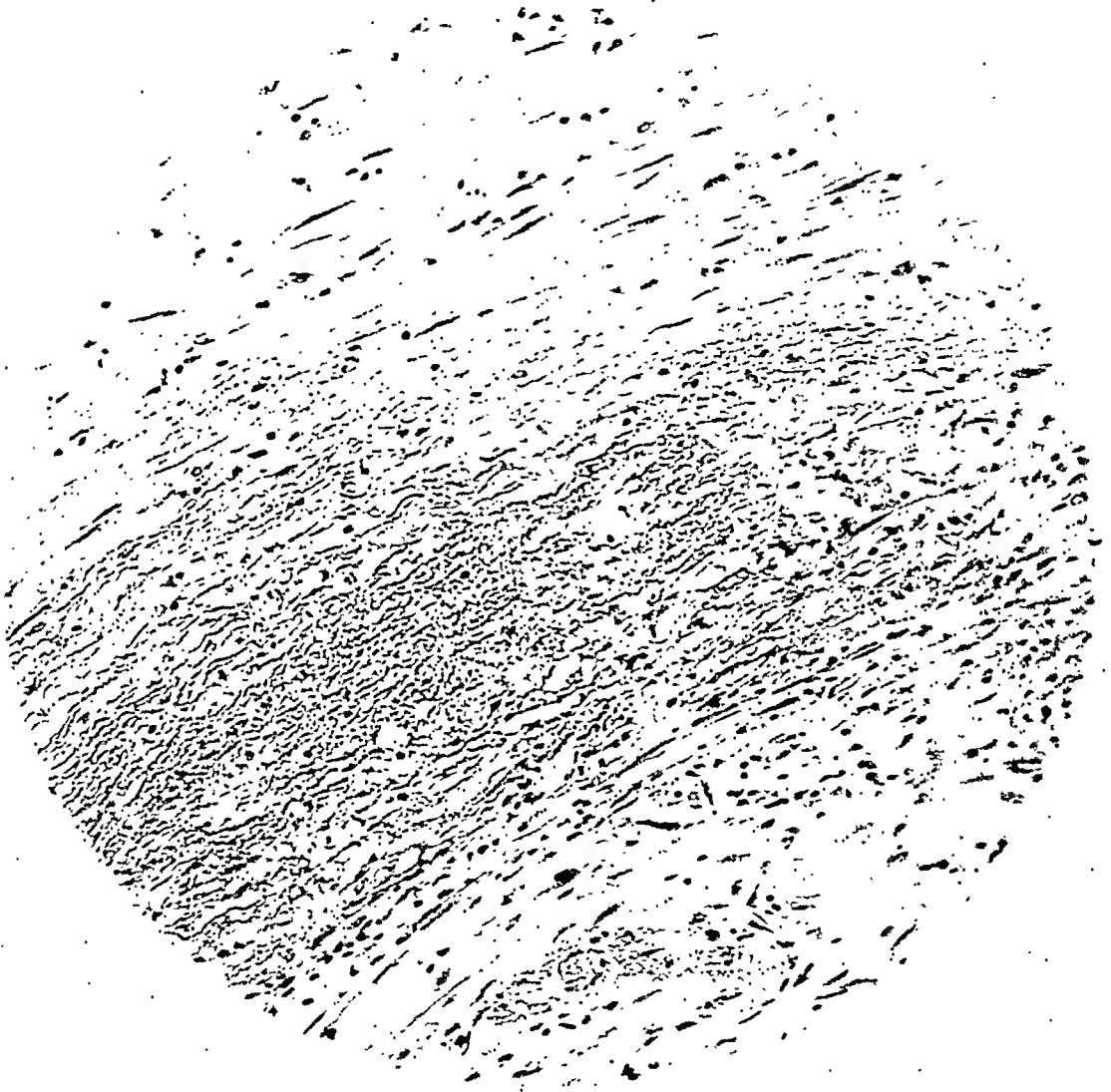


FIG. 3. (Case 31). Acute medial necrosis of the proximal portion of the right coronary artery in a case of acute coronary insufficiency in which the coronary arteries were normal to naked eye inspection.

This type of lesion is generally considered to be toxic and not infectious in nature. In both these cases there was an intense chronic purulent bronchiolitis with tubular bronchiectasis. The myocardial lesion was similar to the changes seen at the periphery of an acute infarction due to coronary thrombosis. Table 3 summarizes the cases of toxic myocarditis.

There was presumptive evidence of a toxic factor producing myocardial damage in six other cases. In two the lesion was similar to that observed in the case of acute pneumonia. One case was an instance of combined syphilis and hypertension. There were two foci of chronic active infection which may have been the source of toxic products, chronic purulent bronchiolitis with bronchiectasis and chronic pyelonephritis. The other case, a child,

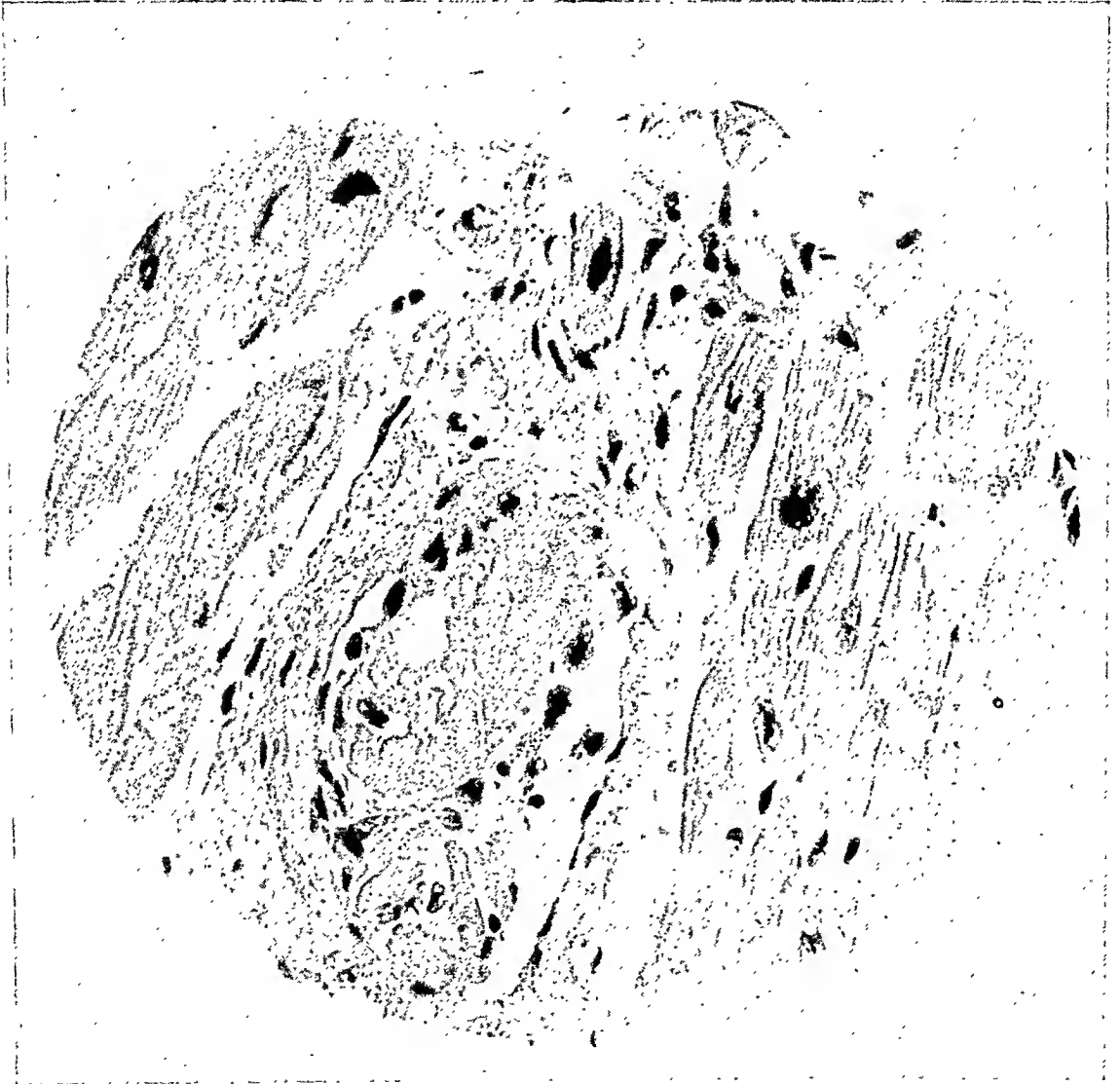


FIG. 4. (Case 6.) Arteriolar thrombi found with acute endocarditis and acute miliary infarctions.

had had a previous infection although none was demonstrable at autopsy. He had entered the hospital with an acute pharyngitis and cervical adenitis and was running a slight fever of 99.6 to 100 degrees. The infection was subsiding and the child gaining weight when a sudden attack of cyanosis and dyspnea occurred with death in a few minutes. The lungs showed no changes. The neck organs were not examined.

TABLE IV  
Myocarditides of Presumptive Toxic Nature

Serial No.	Race	Sex	Age	Group	Under Observation	Anatomical Diagnoses	Remarks
14	W.	M.	58	Combined syphilis and hypertension	1 m	Acute military infarctions of heart. Acute infarctions of kidneys. Chronic purulent bronchiectasis. Syphilis of aortic arch.	Death in anginal attack.
16	B.	M.	68	Combined syphilis and hypertension	10 m	Acute interstitial myocarditis. Chronic purulent bronchiectasis. Chronic pyelonephritis. Commissural syphilis of aorta.	Congestive failure.
22	B.	F.	75	Acute coronary thrombosis	2 w	Recent coronary thrombosis. Chronic purulent bronchiectasis.	Slight dyspnea for 4 yrs.
25	W.	M.	59	Acute coronary thrombosis	5 m	Recent coronary thrombosis. Chronic purulent bronchiectasis.	Clinically improving.
29	W.	M.	70	Acute coronary insufficiency	13 m	Acute military infarctions of heart. Chronic purulent bronchiectasis. Chronic prostatitis.	Compensated for 3 mos.
37	W.	M.	8	Infancy and childhood	2 d	Acute and subacute myocarditis.	Preceding acute pharyngitis, cervical adenitis, cough and low temperature. Clinically recovering.

In two cases the myocardial lesions were of the miliary infarction type. One was a case of combined syphilis and hypertension and one an example of acute coronary insufficiency. Both had the same marked chronic bronchiolitis and bronchiectasis as found in the two previous cases. Multiple kidney infarctions were found in the syphilitic patient. The case of

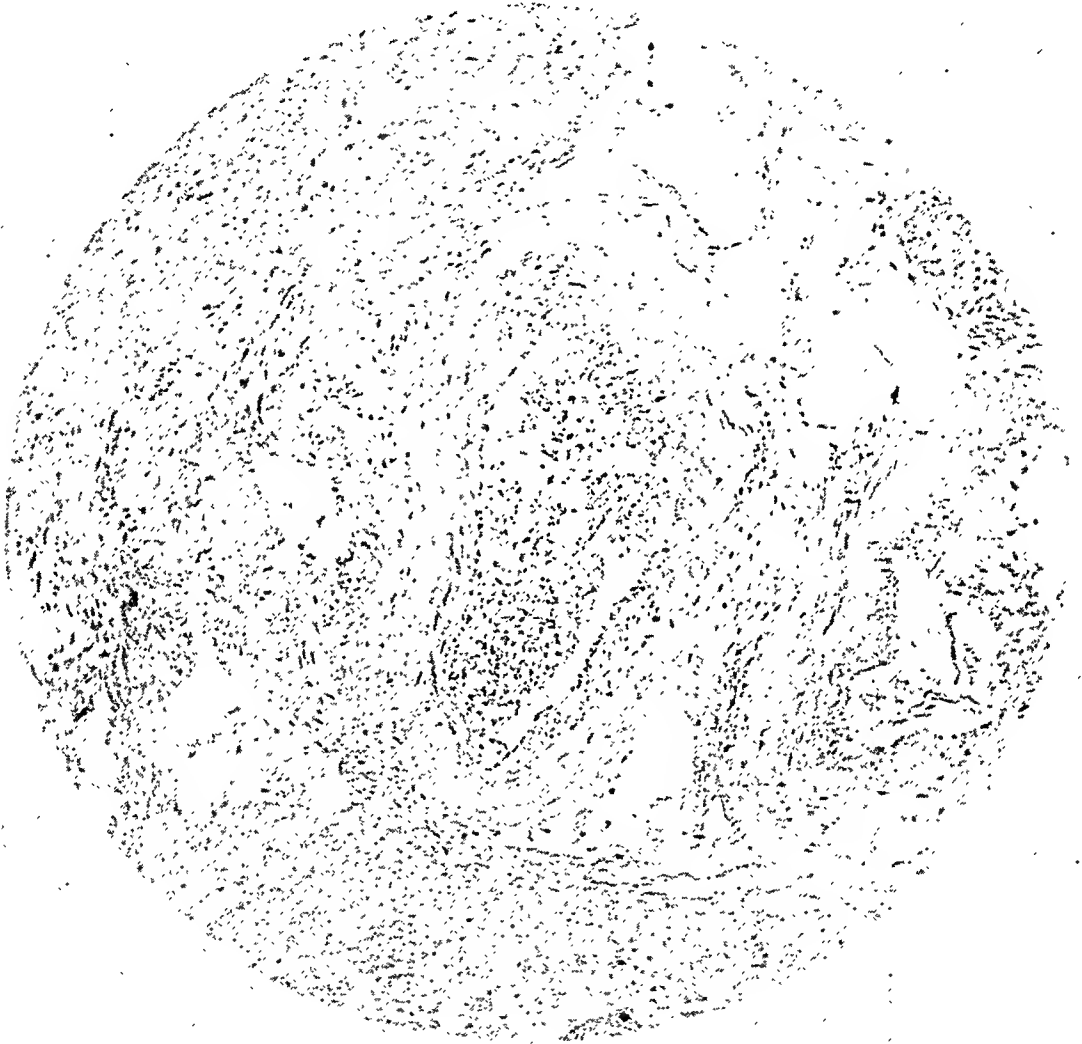


FIG. 5. (Case 30.) Bacterial masses found in the intrinsic arteries of the left ventricle and interventricular wall in a case of acute coronary insufficiency.

acute coronary insufficiency had been compensated for three months. In addition to the chronic pulmonary infection there was a chronic prostatitis.

Two of the cases of acute coronary thrombosis were likewise similar. They also presented the same marked purulent bronchiectasis found in the other cases but again no acute pneumonia was demonstrated. In neither one was there any marked cardiac symptomatology. The first case was a

negro of 75 who had been slightly dyspneic for four years. The second one was a white man who was clinically improving from an anginal attack which had occurred a few days previously. This group of cases of myocarditis of presumptive toxic nature is summarized in table 4.

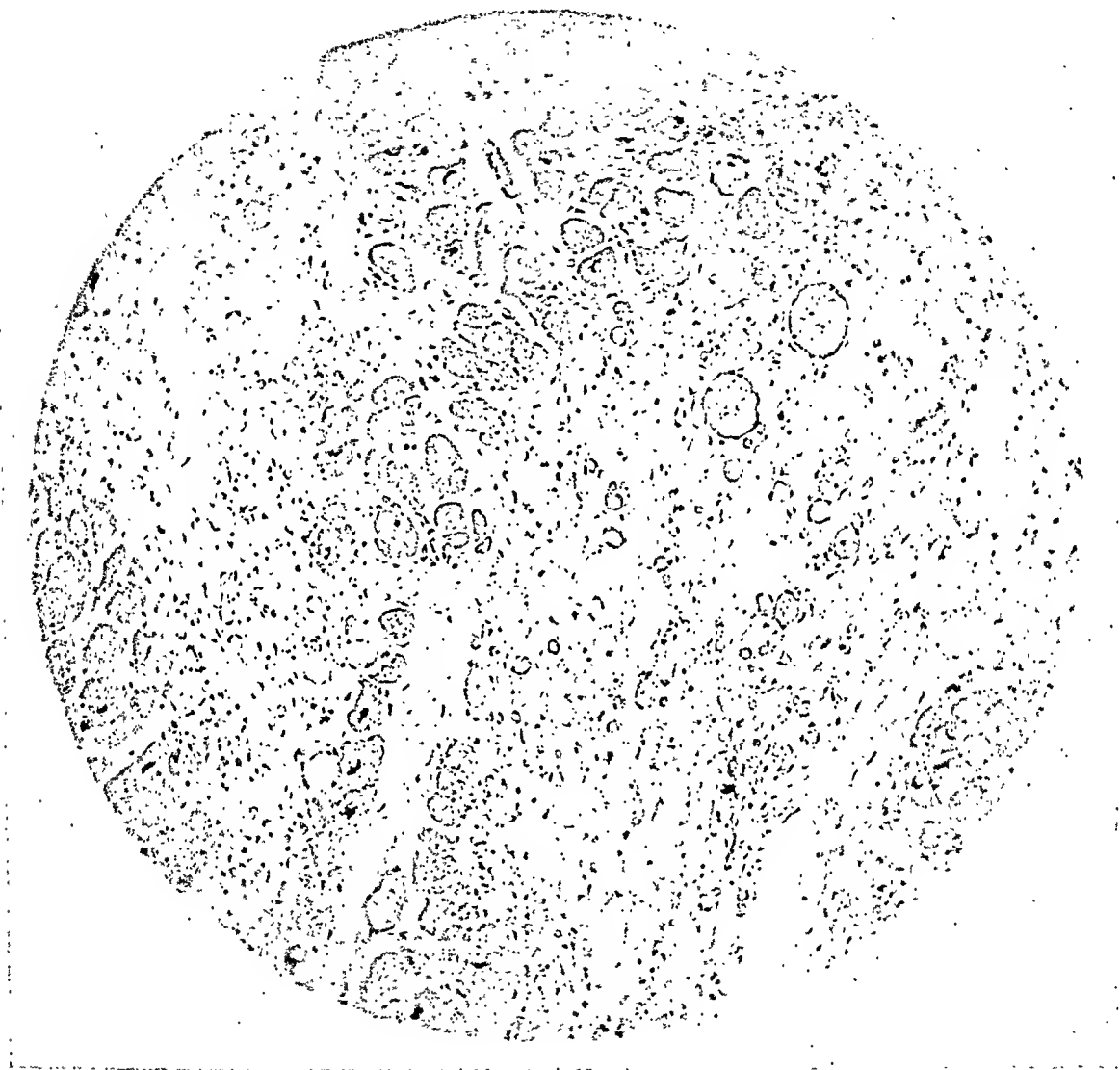


FIG. 6. (Case 6.) Acute miliary infarction.

In the seven remaining cases no factor of infection could be demonstrated. Six were cases of acute coronary thrombosis and one was a child with rickets.

#### DISCUSSION

The important rôle that infection played in this series of cases was unexpected. There were 14 cases that showed an infection in the myocardium, 12 who exhibited toxic changes in the muscle and there was presumptive evidence of a toxic factor producing myocardial damage in six other cases.



It is generally believed that the most frequent basis of acute cardiac death is arteriosclerosis of the coronary arteries. In this series arteriosclerosis was a minor factor.

The distribution of the acute myocardial lesions offers an anatomical basis for the physiologic mechanism of sudden death. The explanations usually advanced are heart block, and ventricular fibrillation. In the cases of Neisserian infection the lesions were concentrated largely in the inter-auricular wall affecting the region of the auriculo-ventricular node. Its destruction could well be the basis of a sudden heart block. In the other cases the lesions were largely concentrated in the ventricles, sometimes more on the left than on the right side and occasionally affecting the deep layer of muscle more than the others. Since acutely damaged muscle is hyper-irritable, it is possible that the widely distributed lesions may have been foci of ectopic beats and by their summation led to the occurrence of ventricular fibrillation.

### CONCLUSIONS

1. The pathologic changes in the heart in 41 cases of sudden cardiac death are reviewed.
2. Acute myocardial changes were demonstrated in 39 hearts.
3. Arterial changes of sclerotic nature played the major rôle in six cases only.
4. An infectious process directly affecting the myocardium was present in 14.
5. A toxic process causing myocardial damage, secondary to acute pneumonia was present in 12.
6. Myocardial damage, possibly toxic, was present in six. In five the source was probably a chronic pyogenic pulmonary infection; in the sixth, an acute upper respiratory infection.
7. Myocardial damage of undetermined etiology was present once.
8. Two cases presented no demonstrable changes sufficient to explain the death.
9. An anatomical basis for sudden heart block and ventricular fibrillation is suggested.

# PNEUMONIA ASSOCIATED WITH PREGNANCY \*

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PNEUMONIA is one of the rare complications of pregnancy. Among about 15,000 obstetrical patients in the Lying-In Hospital during the past five and one-half years pneumonia has been seen only 15 times during the period of gestation. The marked seasonal and other variations in the natural course of this infection make it extremely difficult to compare the disease occurring in pregnant and non-pregnant women. Most of our knowledge is therefore based on what we know about pneumonia as an infectious disease and on the effect of infectious diseases on pregnancy.

For the present report the larger series of cases of pneumonia during pregnancy will be reviewed and the cases seen in the clinic will be analyzed.

In 1905 Ransdell<sup>1</sup> saw two cases and carefully reviewed the literature on the subject for the previous 200 years. From the German, French, Italian, and English he was able to collect 350 cases. No distinction was made between broncho- and lobar varieties. During the first six calendar months of gestation 144 cases were reported of which 22 per cent died and 52 per cent aborted. During the last three months of pregnancy there were 164 cases of which 30 per cent died and 70 per cent delivered. Forty per cent of infants born at a viable age died. Labor seemed to have an unfavorable effect on the maternal mortality; only 10 per cent of patients who did not go into labor died while 36 per cent of those who delivered did not recover.

A large number of cases of pneumonia associated with pregnancy were seen during the influenza year 1918. These were not the ordinary endemic type of pulmonary disease. The pathological studies of Opie, Blake, Small, and Rivers<sup>2</sup> showed that in addition to a large number of pneumococcal lobar pneumonia cases in 1918 there were more than the usual number of hemolytic streptococcus pneumonias, bronchopneumonias and other forms. Pneumonia was present in all fatal cases of influenza.

From questionnaires Harris<sup>3</sup> collected data on 1,350 cases of influenza associated with pregnancy and found that 50 per cent of them developed pneumonia, half of whom died. The mortality was about 60 per cent during the last trimester of pregnancy and about 40 per cent during the first two. Pregnancy was interrupted in 50 per cent of the pneumonias and the mortality was higher (63 per cent) in those who went into labor than in those who did not (41 per cent). However, not all of the most ill patients aborted, for 38 per cent of the patients died undelivered.

The figures reported by Harris show a generally higher mortality than

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those of Ransdell, a result to be expected since it is usually agreed that influenza increases the seriousness of pneumonia. However, the two series give generally similar results. The mortality was highest late in pregnancy and seemed to be increased by delivery. In both reports there was a higher incidence of pneumonia during the last trimester of pregnancy than during the first two, and the apparent difference is exaggerated by making allowance for the six months in the first two trimesters compared with the three months of the last trimester. This greater incidence of pneumonia toward the end of pregnancy is probably more apparent than real, for as Harris<sup>3</sup> has pointed out, many of the pneumonias in early pregnancy are not seen by obstetricians.

In his recent book, "The Management of the Pneumonias," Bullowa<sup>4</sup> reports 71 cases of pneumonia during pregnancy, and they are divided into those occurring before the seventh month and those after that date. In 31 occurring in the last two months of pregnancy the maternal mortality of 23 per cent and fetal mortality of 28 per cent are lower than during the first seven months of gestation where the maternal mortality was 30 per cent and the fetal mortality was 43 per cent. These results are quite contrary to those of Ransdell<sup>1</sup> and Harris,<sup>3</sup> and the reason for the discrepancy is not clear. Bullowa's series may represent a more complete picture of pneumonia in pregnancy than the others; at least he has a larger proportion of cases occurring early in pregnancy, and it is only reasonable to expect the highest fetal mortality at this time. The differences in maternal mortality could be explained by the natural variation in the severity of the disease.

Bullowa's cases are classified according to the type of organism etiological for the disease and his findings are shown in table 1. They follow the usual distribution seen for pneumococcus pneumonias with the possible exception that there are fewer Type II cases than are usually seen in otherwise healthy women under 50. It is interesting and possibly significant that 22 of Bullowa's 71 cases were not pneumococcal pneumonias. Pneumonia occurring at this age is fundamentally lobar in type, and Cecil<sup>5</sup> found pneumococci responsible for 95 per cent of lobar pneumonia cases. Bronchopneumonia is most often a disease of the debilitated, and it may be that in certain women pregnancy acts as such a condition.

The 15 cases of pneumonia during pregnancy seen in the New York Hospital are summarized in table 2. They occurred from the twenty-fourth to the fortieth week of gestation and all but one of them were lobar in type. Pneumococci were isolated from the sputum of all but one. In this case, although the clinical findings were those of lobar pneumonia *Staphylococcus albus* was the only organism consistently recovered. Type XVIII pneumococcus and a Friedländer bacillus were found in the sputum of the patient with signs and roentgen-ray evidence of bronchopneumonia. There were four Type I cases, one Type II, and one Type III, and one organism was Type VIII or an atypical III. Seven had Group IV pneumococcus, and in the more recent of these where this group was further classified, a Type XVIII was identified. Six patients had positive blood cultures, but in only

TABLE I  
Pneumonia Cases Reported by Bullova

Pregnancy More Than 7 Months			TYPE	Pregnancy Less Than 7 Months		
Number	Maternal Mortality	Fetal Mortality		Number	Maternal Mortality	Fetal Mortality
7	1	1	I	12	4	5
2	1	1	II	2	1	2
			III	5	3	3
1	0	0	IV			
1	1	1	V			
			VI	1	0	0
2	1	1	VII	1	1	1
1	0	0	VIII	2	0	1
1	0	0	IX	2	1	1
			XII	1	0	0
2	0	0	XIV	1	1	1
			XV	1	0	0
1	0	0	XVII			
1	0	0	XX	1	0	0
1	0	1	XXIII			
11	3	3	Non-pneu- mococcus	11	1	3
31	7 23%	8 28%		40	12 30%	17 43%

two of these was the culture strongly positive and both of these patients died. The outcome in the others did not seem related to the blood culture findings. Of the five cases for which therapeutic serum was available three were treated. Two had allergic histories, one of whom was found to be sensitive to horse serum.

The most interesting finding on this chart is related to the history of preceding common colds. Ten of the 15 patients had common colds before the onset of their pneumonias, and in two others the data are incomplete, so that there were only three patients with no definite evidence of a preceding respiratory tract infection. Several had colds for two to four weeks before they developed pneumonia. One patient assisted in the care of her husband who had Type I pneumonia 12 days before she developed a fatal case of the same disease.

Four of the 15 patients recovered from pneumonia without going into labor and two others died undelivered. The remaining nine patients delivered during the course of their disease. The day of delivery after the onset of pneumonia is shown in table 3. The much larger series of Ransdell<sup>1</sup> gives a more complete picture than our few cases of the day of disease on which delivery occurs. His results are shown in the same table. Most of his cases delivered within the first six days but delivery apparently can occur at any time. Some allowance should be made for the fact that many cases have recovered by the seventh day of the disease.

TABLE II  
Pneumonia Cases Observed at New York Hospital

History Number	Week of Gestation	Type of Involvement	Type of Pneumococcus	Preceding Common Cold	Blood Cultures	Maternal Result	Remarks
44094 143468	24 28	Lobar Lobar	I XVIII	Yes Yes	1 col. per c.c. Negative	Recovery Recovery	Asthmatic. Died 1 mo. later. 4 hrs. P.P. of cryptogenic, erythroblastic splenomegaly.
86086	29	Lobar	I	Yes	385 col. per c.c.	Death	Hay fever and positive skin test. Husband had Type I pneumonia 12 days before patient.
16899 154234 182430	30 30 31	Lobar Lobar Lobar	Group IV III Group IV	Not known Yes No	800 col. per c.c. Negative Negative	Death Death Recovery	Pneumonia during course of severe pyelitis.
42750	34	Lobar	Group IV	Yes	Positive in broth only	Recovery	
58422 56489 117496	36 36 36	Broncho Lobar Lobar	XVIII and Friedländer I VIII or Atypical III	Probably No No	None 5 col. per c.c. 5 col. per c.c.	Recovery Death Recovery	85,000 units serum. Delayed resolution.
155432 107191 13143 97580	37 38 39 40	Lobar Lobar Lobar Lobar	<i>Staphylococcus albus</i> Group IV Group IV I	Yes Yes Yes Yes	Negative Negative Negative Negative	Recovery Recovery Death Recovery	Complicated by otitis media; 82,500 units serum A.P., 57,000 units serum P.P. Serum on 2 occasions.
28894	40	Lobar	II	Yes	Negative	Recovery	
		14 Lobar 1 Broncho	I-4; II-1; III-1; III or VII-1; Group IV -7	10 Yes		10 Recovery 5 Death	

TABLE III

Day of Pneumonia on Which Delivery Occurred

Day of Pneumonia	1	2	3	4	5	6	7	8	9	10	11+
Number of Deliveries	2	3	1	2	1						
N. Y. H. Series											
Ransdell's Series	7	18	27	12	16	10	8	3	5	2	13

The effect of pneumonia on the labor and on the fetus can be analyzed from the data in table 4. The estimated week of gestation is listed in column two and the birth weight of the fetus in column three. There is good agreement between the data in these two columns. The duration of the present and of previous labors is recorded in columns four and five. Labor was short when premature infants were born and in most instances was shorter than with the previous pregnancies. In several instances full-term infants were delivered in a surprisingly short time. In others labor seemed to be quite normal, lasting 21 hours in one case. Another patient had mild pains for 82 hours and made no progress. When her pneumonia became severe, labor became very active and she delivered in an hour.

Fetal mortality is generally considered to be high when pneumonia complicates pregnancy. Ransdell<sup>1</sup> states that 41 per cent of infants of viable age die although he does not specify in detail the age and size of the infants. Bullowa<sup>4</sup> had seven deaths among 25 infants born after the seventh month of gestation, a mortality of 28 per cent. Five of these 25 infants had positive blood cultures but three of the infants with positive blood cultures lived. This seems rather surprising as intrauterine infection has been considered one of the major causes of fetal mortality. Toxemia and anoxemia have also been considered harmful to the fetus.

In contrast to the above results the pneumonia seemed to be a relatively unimportant cause of fetal death in our series. Three infants, all of whom weighed less than 1,660 gm., died or were still-born. One of them had a negative blood culture although his mother's blood culture was strongly positive. All of the infants sufficiently large to have a reasonable chance to survive, recovered. There were six of these infants, all of whom weighed more than 2,300 gm. and who were estimated to have had 36 or more weeks of uterine existence. These findings suggest that prematurity is the major cause of fetal mortality in the pneumonia of pregnancy. A larger series of cases will be necessary to verify this finding.

The management of our cases differed little from that given to other pneumonias. Cyanosis was decreased by oxygen administration and most patients delivered in an oxygen tent. There were others, however, in whom cyanosis was too slight to need treatment even during labor. In many writings on the subject emphasis is placed on the avoidance of pituitrin and other drugs which stimulate uterine contractions in the treatment of the pneumonia of pregnancy. In only one of our cases was dis-

TABLE IV  
Duration of Labor and Fetal Mortality at New York Hospital

History Number	Week of Gestation	Birth Weight of Fetus	Duration of Labor	Duration of Preceding Labors	Fetal Result	Maternal Result	Remarks
44094	24	760	2 $\frac{4}{60}$	1—24 hours 2— 3—10 hours 4—12 hours	Stillborn	Recovery	
143468 86086	28 29	1650	Did not deliver during pneumonia 4 $\frac{5}{60}$	1—Version pneumonia recovery 2—Abortion 2 months 3—Abortion 2 $\frac{1}{2}$ months 4—Forceps	Died 1 day old	Recovery Death	Maternal blood culture 385 col. per c.c. Fetal blood culture negative.
16899 154234	30 30	1660	Died undelivered 3 $\frac{7}{60}$	None	Died 1 day old	Death Death	Maternal blood culture negative.
182430 42750 58422 56489 117496	31 34 36 36 36		Did not deliver during pneumonia Did not deliver during pneumonia Did not deliver during pneumonia Died undelivered 1 $\frac{4}{60}$			Recovery Recovery Recovery Death Recovery	
155432 107191	37 38	2430 3240	1 $\frac{1}{60}$ 21 $\frac{4}{60}$	1—6 hours 2—6 hours 3—6 hours None 1—24 hours 2—24 hours 3—Abortion 3 weeks 1—9 hours	Lived Lived Lived	Recovery Recovery	
13143	39	3145	1		Lived	Death	Mild labor without progress 82 hours before onset of real pains.
97580	40	3440	71 $\frac{9}{60}$	1—22 hours 2—12 hours 1—7 hours	Lived	Recovery	
28894	40	2930	53 $\frac{2}{60}$	2—3-4 hours 3—3-4 hours 4—3-4 hours 5—3-4 hours 6—3-4 hours 7—3-4 hours	Lived	Recovery	

tention marked before delivery and it was readily relieved by enemas and turpentine stupes. It is also considered advisable to delay labor since the mortality seems to be highest in patients who deliver. It is reasonable to expect that the work required for delivery would lessen the chances of recovery of any pneumonia patient. It seems evident from reviewing these cases, however, that the obstetricians have little control over the onset of uterine contraction and that most patients go into labor in spite of precautions to prevent it.

There are scant data from which to evaluate the use of serum in the pneumonia of pregnancy. Bullova<sup>4</sup> believed that some mothers and infants survived as a result of serum treatment, and recommends its use as early as possible in the disease. In 27 cases in which serum was given the maternal mortality in his series was 37 per cent. Doubtless many of these were very ill patients for in the cases not given specific serum the mortality was 20 per cent, and only 30 per cent of the pneumococcal pneumonias who did not get serum died. These results are rather disappointing but the series is much too small to give a real picture of the value of therapeutic serum. Bullova observed no harmful effects from serum and its administration did not induce labor in any case.

In addition to the cases just discussed, five of our patients developed pneumonia early in the puerperium. Four of these had common colds at the time of delivery and several of them may have had early pneumonia. All had non-operative deliveries without anesthesia. One was found to be febrile immediately post-partum; one had a chill 12 hours after delivery; another had a chill and bloody sputum on the first post-partum day; a fourth patient had signs of consolidation 17 hours after delivery; and a fifth had similar signs on the fourth post-partum day. All patients recovered except one who died of Type II pneumococcus bacteremia on the fifth post-partum day.

These patients were separated from the previously described group because the presence of pneumonia was not established before delivery. Possibly some of these should have been considered pneumonia during pregnancy in which the patients went into labor early in the disease. It is interesting to note that pneumonia was diagnosed in the first five days of the puerperium in one-third as many instances as it was seen during the entire 40 weeks of pregnancy and that it was preceded by a common cold in almost every instance.

#### SUMMARY AND CONCLUSIONS

In summarizing this study we find that pneumonia is an infrequent but serious complication of pregnancy. Once it has developed it is very similar to pneumonia in non-pregnant women. It is difficult to establish that the mortality is appreciably altered by the presence of pregnancy. Patients may die or recover undelivered, but in the majority of instances they go into



labor. Labor is apt to develop early in the disease but may begin late. It is frequently of short duration but may run the usual course. If the infant is of sufficient size and age, it will probably live.

Common colds usually precede the development of pneumonia during pregnancy and pneumonia is apt to develop during the puerperium in patients who have common colds at the time of labor. The adequate treatment of a common cold during pregnancy is an important way of preventing pneumonia during pregnancy and the puerperium.

The management of the pregnant patient with pneumonia is essentially the same as the management of any pneumonia patient. There are insufficient data for determining the value of specific treatment in the therapy of the pneumonia of pregnancy.

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# UNSUSPECTED CORONARY THROMBOSIS IN PATIENTS WITH HEMIPLEGIA—A CLINICAL STUDY \*

By DANIEL L. DOZZI, M.D., *Philadelphia, Pennsylvania*

IN A recent report<sup>1</sup> reviewing 1000 consecutive, unselected autopsies for the incidence of coronary thrombosis in patients dying with a diagnosis of a cerebrovascular accident, it was found that of the 1000 cases, there were 107 with either cerebral hemorrhage, cerebral thrombosis or cerebral embolism. Of these 107, there were 12 that had a coronary thrombosis in addition to the cerebral lesion; but the cardiac condition had not been diagnosed antemortem in a single case.

During the study of the 1000 autopsies, there were found 41 cases of established coronary thrombosis. Since 12 of these were undiagnosed and were complicated by a cerebral lesion; it would appear that 29 per cent of the cases with coronary thrombosis were masked by the predominating symptoms of an acute cerebral catastrophe. In the previous report it was pointed out that these figures vary considerably from those in the literature. Mention was also made that the usual reports deal with the incidence of cerebral embolism as a complication in patients known to have coronary thrombosis, whereas the report under discussion was concerned with the frequency of unsuspected, undiagnosed coronary thrombosis in patients with an antemortem diagnosis of cerebral thrombosis, cerebral hemorrhage or cerebral embolism.

In view of the autopsy findings in the previous report and because the method of study yielded different figures from those usually encountered in the literature, it was decided to study a group of clinical cases in an attempt to establish the true relationship between coronary thrombosis and cerebral embolism.

## METHOD OF STUDY

All patients presenting themselves with evidence of a cerebrovascular accident, chiefly hemiplegia, were studied in the usual manner, and in addition routine electrocardiographic tracings with four leads, teleoroentgenograms of the heart when possible and occasionally the venous pressure were recorded. Patients that succumbed to their illness were submitted to post-mortem examination when feasible. The material to be presented was obtained from three different sources:

† I. From the neurological service of the late Dr. Clarence A. Patten at the Philadelphia General Hospital.

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† Through the courtesy of the late Dr. Clarence A. Patten.

- † II. From the neurological service of the late Dr. Clarence A. Patten at the Lankenau Hospital.
- ‡ III. From the medical service of Dr. George M. Piersol at the Graduate Hospital, University of Pennsylvania.

### CORONARY THROMBOSIS UNSUSPECTED IN PATIENTS WITH HEMIPLEGIA

There were 66 patients studied; 25 did not recover from their illness and 15 of these had a postmortem examination.

Material obtained from	No. of cases with a cerebrovascular accident	No. of foregoing cases with coronary thrombosis	Percentage with cerebral and cardiac lesion
Lankenau Hospital . . . . .	11	1	9%
Philadelphia General Hospital . . . . .	40	5	12%
Graduate Hospital . . . . .	15	2	13%
Above combined (total) . . . . .	66	8	12.1%

It will be noted from the above table that 12.1 per cent or 8 of the 66 cases studied, had coronary thrombosis in addition to the cerebral lesion.

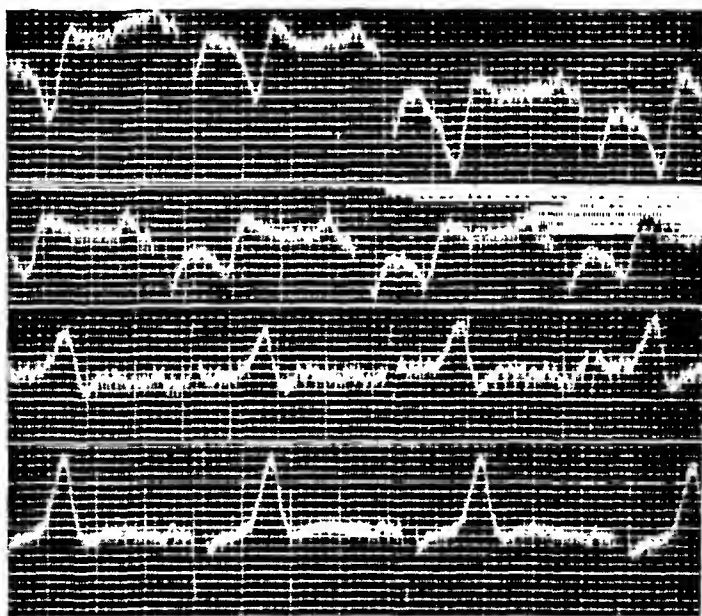


FIG. 1. Electrocardiograph tracing in Case 1.

Rate 70.

P-R 0.16 second.

QRS 0.08 second.

T<sub>1</sub>, T<sub>2</sub> exaggerated in size and deeply inverted.

† Through the courtesy of the late Dr. Clarence A. Patten.

‡ Through the courtesy of Dr. George M. Piersol.

The incidence of the association of the two lesions varied slightly at each hospital. The diagnosis of coronary thrombosis was verified by autopsy in four instances. Two of the cases of coronary thrombosis were of recent origin with some myomalacia. The other two cases were of long standing as evidenced by healing and the presence of mural thrombi. In all four cases it was difficult to state whether the cerebral lesion was a thrombosis or embolism. One of the cases wherein the cardiac lesion was of long standing was difficult to classify antemortem, in that there was some uncertainty as to whether the changes in the electrocardiographic tracings were due to an old, healed coronary thrombosis, or due to a marked coronary sclerosis.

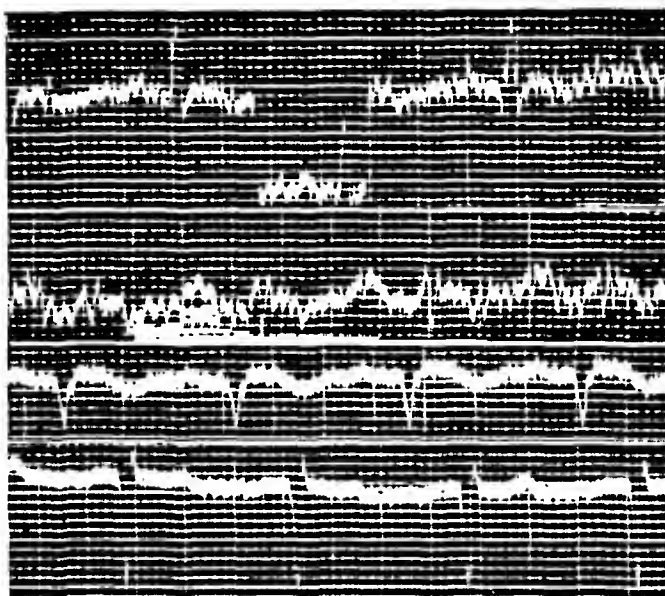


FIG. 2. Electrocardiographic tracing in Case 2.

Rate 90.  
N. S. R.  
P-R—prolonged.  
QRS 0.08.  
 $T_1$ ,  $T_2$ ,  $T_3$  inverted.

There was nothing characteristic about the history or any of the clinical findings which would lead one to suspect the presence of coronary thrombosis. Six of the patients were males and they were from 50 to 60 years of age. Some of the patients were aphasic when admitted to the hospital, thereby making it necessary to rely upon information obtained from other sources. Occasionally, a history was obtained of previous acute precordial or substernal pain, which the patient had failed to mention during the first interrogation. One of the eight patients with both coronary thrombosis and cerebral thrombosis gave a definite history of having had coronary thrombosis one year previous. None of the eight cases was diagnosed as having coronary thrombosis until the routine studies were completed. One

of the other patients in the group of 66 gave a history of an antecedent coronary thrombosis without demonstrable evidence at the time of the study.

It was pointed out in the previous report <sup>1</sup> that perhaps the cerebral lesion is induced by the fall in blood pressure subsequent to the coronary thrombosis, or that both the cerebral and cardiac lesions are merely coincidental to the same pathological process in the respective arteries. Attention has been called to painless coronary thrombosis by East et al.,<sup>2</sup> and recently by Boyd and Werblow.<sup>3</sup> Parkinson<sup>4</sup> states that dyspnea may take the place of pain when coronary thrombosis develops in a patient with cardiac decompensation.

### CASE REPORTS

While it was previously stated that there is nothing characteristic in the history or clinical findings to make one suspect coronary thrombosis in patients with hemiplegia, it would seem fitting to present a typical example of a patient with both a cerebral and a cardiac lesion, and of another with a cerebral lesion without evidence of coronary thrombosis.

*Case 1.* H. M., a white male, aged 61 years, was admitted to the service of Dr. Piersol at the Graduate Hospital, December 28, 1934. Physical examination revealed a right-sided hemiplegia, and the patient manifested difficulty in swallowing. Examination of the heart was essentially negative except for some enlargement of the area of precordial dullness to the left. The blood pressure 230 systolic and 140 diastolic. The past history was inconsequential other than the occurrence of a mild left-sided hemiparesis in June 1934, with complete recovery. Routine electrocardiographic tracing revealed evidence of unsuspected coronary thrombosis. The patient was very ill, but recovered and was discharged February 3, 1935.

*Case 2.* J. D., a white male, 53 years of age, was admitted to the service of Dr. Piersol at the Graduate Hospital, February 7, 1935. Physical examination revealed a left-sided hemiplegia. Examination of the heart was essentially negative. The blood pressure was 170 systolic and 90 diastolic. Past history—"Stroke in October 1934." Frequent attacks of "pain in chest." Routine electrocardiographic studies revealed strain on the left ventricle and coronary disease. Uneventful recovery. Discharged February 20, 1935.

It is seen from the likeness of the two cases presented that without detailed, routine studies of the heart, it is most difficult to ascertain which case of hemiplegia is likely to be complicated by an unindicated coronary thrombosis. In view of these findings and those previously reported, it appears that we have not been aware of the frequency of coronary thrombosis in patients with hemiplegia. This seems to be particularly true in the white male 40 or more years of age.

In the autopsy material the incidence was 12 cases out of 107, or 11.2 per cent. The studies on the clinical material reveal an incidence of 12.1 per cent. While these two studies tend to substantiate one another, the results differ from those of other writers. Parkinson et al.<sup>4</sup> refer to embolism as a complication of coronary thrombosis and out of 83 cases autopsied,

found cerebral embolism in one case, an incidence of 1.2 per cent. Meakins and Eakin<sup>5</sup> report the autopsy findings of 62 cases with coronary occlusion and state that 6.4 per cent had a cerebral thrombosis. Conner and Holt,<sup>6</sup> in reviewing 287 cases with coronary thrombosis, state that 14 had developed cerebral embolism and two developed signs of cerebral thrombosis many months after the attack of coronary thrombosis. In their series the incidence was approximately 5 per cent.

### SUMMARY

Sixty-six patients with hemiplegia were studied for the incidence of coronary thrombosis. It was found that 8 or 12.1 per cent of these patients with hemiplegia also had coronary thrombosis and that the latter lesion would not have been diagnosed were it not for the routine inclusion of detailed heart studies in the examination of all patients with hemiplegia, irrespective of history or clinical findings. While these figures compare favorably with the previously reported incidence of 11.2 per cent based on autopsy material, these results vary considerably from those of other workers.

Although there is nothing characteristic about the history or clinical findings of the hemiplegic who is prone to have an unindicated or latent coronary thrombosis, the incidence is definitely greater in the white male beyond 40 years of age. The majority are between 50 and 60 years. It was pointed out that the cerebral lesion may be induced by the drop in blood pressure secondary to the coronary thrombosis, or that both lesions may be due to the same pathological process in the respective arteries. Mention was also made of the atypical forms of coronary thrombosis. There may be practical value in recognizing the association between coronary thrombosis and cerebral embolism from a therapeutic and prognostic point of view.

The author acknowledges indebtedness to the late Dr. Clarence A. Patten for his cooperation in obtaining the material used for this study.

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# THE DEVELOPMENT OF ARTERIOSCLEROSIS IN THE DIABETIC, BASED ON THE STUDY OF A GROUP OF PATIENTS DURING TEN TO THIRTEEN YEARS\*

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BOTH clinical and pathologic data support the view that vascular disease of the atherosclerotic type occurs earlier and is more extensive in the diabetic patient. Now that the proper use of insulin can almost eliminate uncomplicated acidosis as a cause of death and has greatly improved the status of the diabetic patient with an infection, attention, at the present time, is being directed toward the reduction of the intensity of atherosclerosis. The involvement of the muscular arteries, particularly the coronaries and those of the extremities, is responsible for the majority of deaths in older diabetics. Whatever the pathogenesis of this process may be, the majority opinion agrees that it is caused by the diabetes. The Virchow-Aschoff cholesterol imbibition theory of arteriosclerosis, the production of experimental atherosclerosis and the disturbed cholesterol and fat metabolism in diabetes, together form the background for the conception that atherosclerosis in the diabetic is caused by altered fat and cholesterol metabolism. For this reason the use of large amounts of fat in the diabetic diet has been considered by some physicians to be a possible etiologic factor in the production of premature atherosclerosis.

The observations which form the basis of this article are a continuation of similar studies made in 1924<sup>1</sup> and in 1927.<sup>2</sup> In 1924 the lower extremities of a group of diabetic patients were examined for calcification of the arteries by means of roentgenograms; in 1927 the same group was re-studied by the same method, and additional patients were observed. Sixty-three per cent of 167 patients beyond the age of 40 were found to have a degree of calcification that could be detected roentgenologically. In a group of 121 non-diabetic people of the same age, 28 per cent had such calcification. Further, it was believed that the data showed that incomplete control of the diabetes was the most influential factor in the production of this calcification. It also appeared that uncontrolled diabetes over a period of five years was sufficient to produce calcification even in younger diabetic patients. At that time higher fat diets were being used than at present. However, they were not as excessively high in fat as those advocated by

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From the Out-Patient Department of the Buffalo General Hospital.

others during that period. The carbohydrate content was usually from 50 to 100 grams, protein, one gram per kilo of body weight, and fat, 130 to 170 grams daily. The patients in this study were on this moderately high fat diet until 1933–1935, when the carbohydrate content was increased somewhat and the fat reduced. During 1936–1937, we were able to re-study 52 of the patients in the original groups. In addition the adequacy of the circulation of the lower extremities was determined by clinical methods. Particularly we were interested to determine, if possible, the influence of the diet, and further to get additional information on the effect of the methods by which the diabetes had been controlled. Nearly all of these patients were observed with sufficient regularity so that the examiner gained a good idea as to their reliability and coöperativeness. The ratings as to the control of the diabetes were given rather arbitrary designations such as had been employed in the previous studies. The words *excellent*, *good*, *fair*, and *poor* lack the precision which should characterize accurate investigation, but in a long-term observation such as this it is not possible to get more than a general idea with regard to a patient's behavior. It is believed, however, that a physician who personally comes in contact with patients over a long period gets an opinion that is significant. The contributors to this study made their observations independently before the complete data were organized. One of us (B. D. B.) cared for the patients and rated them as to the control of the diabetes. The studies of the circulation of the lower extremities were made in The Peripheral Vascular Clinic by a second observer (J. S. R.) and the roentgenograms were interpreted by a third (E. C. K.). The designations of the degree or extent of visualization of the calcified arteries by roentgenography were the same as was used in previous articles. The patients were divided into three groups and were arranged in chronological order according to the duration of the diabetes.

Group I (table 1) contains 20 patients who were believed to have had their diabetes under *good* or *excellent* control throughout most of their diabetic life. Thirteen were women and seven were men. The average age was 59. Only three of the patients had a stout habitus; the others were either thin or of average body conformation. The average estimated duration of the diabetes was 13.7 years and the average number of years on insulin was 11.7. Three of them did not require insulin and the average daily dose for the others was 32 units. None of the patients had a diastolic blood pressure that exceeded 90 mm. at any time. In 1927 the systolic blood pressure was 150 mm. or over in seven, whereas in 1936–1937 this was the case in nine. Only two of the patients, both women whose ages exceeded 75 years (Cases 12 and 15), showed extensive calcification of the leg arteries; these also showed a marked degree of circulatory deficiency of the lower extremities. Five of the group (Cases 1, 5, 10, 11 and 13) showed questionable deficiency of the circulation of the legs and feet by the method employed, and Cases 6, 9, 19 and 20 had slight but definite objective impairment.



TABLE I (GROUP I)

Control of diabetes estimated as *excellent* or *good* throughout. Averages: Age, 59 years; probable duration diabetes, 13.7 years; years on insulin, 11.7; daily insulin dosage, 32 units. Thirteen women, seven men.

				Probable Duration Diabetes	Insulin		Blood Pressure (mm.)						Calcification			Circulation of Lower Extremities						Clinical Comments		
													(Roentgen-ray) Feet—Legs											
Case No.	Age	Sex	Habitus	Years	Yrs.	Units (24 hrs.)	1924		1927		1936-37		1924	1927	1936-7	Dorsalis Pedis Pulses	Posterior Tibial Pulses	Claudication	Trophic Changes	Dependent Rubor	Elevation Pallor	Circulation Deficiency		
							Sys.	Dias.	Sys.	Dias.	Sys.	Dias.											Sys.	Dias.
1	67	F.	Stout	22	13	24	108	80	155	90	130	70	0	0	0	3+	2+	0	0	0	0	0	0	Cellulitis of foot several times.
2	61	F.	Average	19	14	55			185	50	170	90	0	0	0	—	—							Pulmonary and renal tuberculosis.
3	73	F.	Average	15	13	26			130	80	190	90	0	0	0	2+	2+	0	0	0	0	0	0	Coma, 1924.
4	47	F.	Average	15	14	28			125	80	110	75	0	0	0	3+	3+	0	0	0	0	0	0	Coma, 1924.
5	47	F.	Average	15	13	16			110	80	120	80	0	0	0	4+	4+	0	0	0	0	0	0	Coma, 1925.
6	42	F.	Average	15	13	22			125	85	135	80	0	0	0	0	4+	+	0	0	0	0	0	Feet very sensitive to cold.
7	62	F.	Thin	15	14	40	145	80			133	70	0	0	±	3+	3+	0	0	0	0	0	0	Coma, 1925.
8	60	F.	Average	15	—	—	150	70	165	75	180	70	0	0	0	2+	2+	0	0	0	0	0	0	Hyperthyroidism, 1936.
9	76	F.	Average	14	13	21			150	90	205	80	0	0	0	+	+	0	0	0	0	0	0	

TABLE I (GROUP I)—Continued

				Probable Duration Diabetes	Insulin		Blood Pressure (mm.)						Calcification			Circulation of Lower Extremities						Clinical Comments		
													(Roentgen-ray) Feet—Legs											
Case No.	Age	Sex	Habitus	Years	Yrs.	Units (24 hrs.)	1924		1927		1936—37		1924	1927	1936—7	Dorsalis Pedis Pulses	Posterior Tibial Pulses	Claudication	Trophic Changes	Dependent Rubor	Elevation Pallor	Circulation Deficiency		
							Sys.	Dias.	Sys.	Dias.	Sys.	Dias.											Sys.	Dias.
10	67	M.	Stout	14	12	28			140	85	130	70		0	0	2+	2+	0	0	0	+	+	±	Coronary occlusion, 1936.
11	40	M.	Thin	14	13	50					120	80		0	0	+	4+	0	0	0	2+	+	±	Coronary occlusion, 1928.
12	78	F.	Thin	12	9	18			170	90	180	90		0	2+	0	+	+	+	+	+	+	3+	Very mild diabetes.
13	65	M.	Stout	11	—	—			110	65	135	75		0	+	0	4+	0	0	0	±	+	±	Coronary occlusion, 1936.
14	65	F.	Average	11	9	6	135	80	140	85	150	95	0	0	0	3+	2+	0	0	0	+	+	0	Coronary occlusion, 1936.
15	83	F.	Average	11	10	15			225	90	230	60		3+	3+	0	0	?	0	0	+	+	2+	Died, 1937.
16	65	F.	Average	11	—	—			150	85	160	90		0	0	2+	2+	0	0	0	0	0	0	Unstable blood pressure.
17	62	M.	Average	11	9	23			160	80	190	90		0	0	3+	3+	0	0	0	0	0	0	Coronary occlusion, 1936.
18	50	F.	Average	11	10	65			130	80	115	70		0	0	+	+	0	0	0	0	0	0	
19	35	M.	Thin	11	10	60			130	80	105	70		0	0	0	3+	0	0	0	+	+	+	
20	40	M.	Average	11	10	42			120	80	125	75		0	0	0	4+	0	0	0	+	+	+	

TABLE II (GROUP II)

Control of diabetes estimated as *fair* or *poor* throughout. Averages: age, 55 years; probable duration diabetes, 14.7 years; years on insulin, 9; daily insulin dosage, 36 units. Fourteen women, nine men.

Case No.	Age	Sex	Habitus	Probable Duration Diabetes Years	Insulin		Blood Pressure (mm.)						Calcification (Roentgen-ray) Feet—Legs			Circulation of Lower Extremities							Clinical Comments
					Yrs.	Units (24 hrs.)	1924		1927		1936-37		1924	1927	1936-37	Dorsalis Pedis Pulses	Posterior Tibial Pulses	Claudication	Trophic Changes	Dependent Rubor	Elevation Pallor	Circulation Deficiency	
							Sys.	Dias.	Sys.	Dias.	Sys.	Dias.											
1	78	F.	Stout	21	11	18			160	90	170	80		2+	4+	3+	0	0	+	+	2+	2+	Retinitis.
2	72	M.	Average	18	13	24			150	100	180	100		3+	4+	4+	0	0	2+	2+	3+	3+	Died cerebral thrombosis.
3	82	F.	Average	17	10	20	145	80	165	90	180	100		+	3+	+	0	0	2+	2+	2+	2+	Congestive heart failure.
4	44	M.	Stout	17	13	70			120	80	130	100		+	2+	2+	0	0	0	±	0	0	Peripheral neuritis.
5	42	F.	Stout	17	13	40	80	54	120	85	150	80		+	3+	3+	0	+	2+	2+	3+	3+	Retinitis.
6	69	M.	Stout	17	13	36			120	80	150	80		+	3+	3+	0	+	2+	2+	3+	3+	Died cerebral thrombosis.
7	59	M.	Stout	17	12	60			140	80	140	90		3+	3+	3+	+	+	+	+	2+	2+	Congestive heart failure.
8	55	M.	Average	16	14	50			130	75	140	80		0	3+	0	0	+	3+	3+	3+	3+	Peripheral neuritis.
9	71	M.	Stout	16	—	—	130	70	130	80	170	80	2+	3+	4+	0	0	0	+	+	+	+	Took insulin irregularly.
10	59	M.	Average	15	13	50	106	58	106	58	120	80	0	0	3+	0	±	0	+	+	2+	2+	Died pulmonary tuberculosis.
11	68	F.	Stout	15	9	18	185	90	190	85	170	90		±	4+	0	+	+	+	+	3+	3+	Developed gangrene; retinitis.
12	74	F.	Stout	14	4	16	110	80	170	90	145	85	+	2+	3+	0	+	+	±	+	2+	2+	Coronary occlusion, 1935.

TABLE II (GROUP II)—Continued

Probable Duration Diabetes				Insulin		Blood Pressure (mm.)						Calcification			Circulation of Lower Extremities							Clinical Comments			
																							(Roentgen-ray) Feet—Legs		
												Yrs.	Units (24 hrs.)	1924		1927		1936-37		1924	1927		1936-7	Dorsalis Pedis Pulses	Posterior Tibial Pulses
Case No.	Age	Sex	Habitus	Years	Yrs.	Units (24 hrs.)	Sys.	Dias.	Sys.	Dias.	Sys.	Dias.	Sys.	Dias.	Sys.	Dias.	Dorsalis Pedis Pulses	Posterior Tibial Pulses	Classification	Trophic Changes	Dependent Rubor		Elevation Pallor	Circulation Deficiency	
13	56	M.	Stout	14	13	54			135	90	152	80		0	±	+	+	4+	0	0	±		+	2+	+
14	68	F.	Stout	13	7	30			135	75	210	80		0	3+	0	0	0	0	0	±	+	+	0	Pulmonary tuberculosis, 1936.
15	23	F.	Stout	13	12	50					105	90		0	4+	3+	0	0	0	±	0	0	0	0	Took insulin irregularly.
16	59	F.	Average	13	10	20			135	95	160	90		0	0	4+	0	0	0	0	±	0	0	0	Congestive heart failure.
17	66	F.	Stout	13	—	—	135	80			170	105		0	3+	2+	+	+	0	0	0	0	0	0	Syphilis; varicose ulcers.
18	53	F.	Stout	13	12	60			140	90	140	90		0	0	4+	4+	4+	0	0	0	0	+	2+	Peripheral neuritis; died of infection, 1937.
19	74	F.	Stout	13	—	—	180	90	180	90	160	90		0	+	0	0	0	+	±	+	+	+	0	Peripheral neuritis.
20	50	F.	Stout	12	—	—			132	88	120	70		0	+	2+	4+	4+	0	0	0	0	+	0	Peripheral neuritis; died of infection, 1937.
21	23	F.	Stout	12	11	42					150	80		0	3+	+	+	0	+	0	0	+	0	2+	Peripheral neuritis.
22	60	M.	Average	12	11	22	120	80	125	80	125	80		0	+	2+	4+	4+	0	0	0	0	0	0	Peripheral neuritis.
23	59	F.	Stout	10	8	15			160	80	160	90		0	0	0	0	2+	2+	0	0	±	±	+	Peripheral neuritis.

Group II (table 2) was comprised of the patients who were regarded as uncoöperative. The average age was 55, inclusive of two patients (Cases 15 and 21) who were 23 years old; if these had been omitted the average age would be about the same as that of the patients in Group I. The ratio of men to women was also about equal in the two groups. A stout body habitus predominated in this uncoöperative group; at the present time, however, a number of these patients are thin because of uncontrolled diabetes. The average patient in this group has had diabetes a year longer and has taken insulin two years less than the average patient in Group I. The dosage of insulin was slightly greater. Insulin was not given to three of the patients because it probably would only have increased their appetites. Nine of the 23 patients in this group had been under observation in 1924; two of them had an increase in the systolic blood pressure at that time without any essential change since. In 1927, seven of the patients had systolic blood pressures that were 150 mm. or more. In 1936-1937, 11 patients had an increase in the systolic blood pressure. During this 10 year period, however, there was no noteworthy change in the diastolic blood pressure. Calcification of the arteries of the legs either appeared or was intensified in 19 of the 23 patients. This is conspicuously shown by an analysis of the findings in the roentgenograms taken in 1927 and in those taken in 1936-1937. Fifteen of the 22 patients upon whom we were able to make clinical observations of the circulation of the lower extremities showed definite evidence of impairment of the peripheral circulation.

Group III (table 3) is made up of the patients whose diabetes was inadequately controlled for a period before insulin treatment. The majority of these patients had undergone serious under-nutrition, either from low caloric diets or as a result of severe diabetes. With one exception, Case 2, the control of the diabetes has been excellent since insulin treatment was begun. The average age of the five women and four men in this group was 65. The average estimated duration of the diabetes was 19 years. The average time of insulin therapy was 13 years and the daily insulin requirement, 49 units. One patient had an elevated diastolic blood pressure in 1927 and two in 1936-1937. The systolic blood pressures exceeded 150 mm. in three instances in 1927; these were found to be still more elevated ten years later. Five of the patients of this group were observed in 1924. At that time three of them had calcification of the arteries of the feet and legs. In 1927 the intensity of this calcification had not changed. In 1936-1937 all but two of the patients in this group had developed evidence of calcification. One, Case 6, a physician, had lived on a high fat diet from 1918 to 1926 when insulin became necessary. At that time he was again placed on a high fat diet on which he remained for eight additional years. We were able to study clinically the peripheral circulation of the lower extremities in eight of the nine patients. Only two of them showed a marked disturbance; in the others the disturbance was only slight. The patient who

TABLE III (GROUP III)

Control of diabetes inadequate before insulin but good since. Averages: age, 65 years; probable duration diabetes, 19 years; years on insulin, 13; daily insulin dose, 49 units. Five women, four men.

Probable Duration Diabetes			Insulin		Blood Pressure (mm.)						Calcification			Circulation of Lower Extremities						Clinical Comments					
					Yrs.		Units (24 hrs.)		1924		1927		1936-37		(Roentgen-ray) Feet—Legs			Dorsalis Pedis Pulses	Posterior Tibial Pulses		Claudication	Trophic Changes	Dependent Rubor	Elevation Pallor	Circulation Deficiency
									Sys.	Dias.	Sys.	Dias.	Sys.	Dias.											
1	68	F.	Stout	23	14	46	130	80	160	85	175	80	2+	2+	3+	±	0	0	+	+	0	+	+	Retinitis.	
2	70	F.	Average	20	14	90	140	90	180	100	210	120	0	0	2+	0	0	0	+	+	+	+	+	Poor control of diabetes in recent years.	
3	58	F.	Stout	20	14	60	75	60	120	70	150	80	0	0	+	0	0	+	2+	2+	3+			Cerebral occlusion, 1935.	
4	68	F.	Average	19	14	58	86	72			150	80	0	0	0	0	0	+	2+		+	+	+	Died coronary occlusion, 1937.	
5	59	M.	Stout	19	13	44	145	90	160	90	205	105	2+	2+	3+	2+	2+	0	±	+	±	±	±	Coronary occlusion, 1937.	
6	63	M.	Average	20	12	32			120	70	140	70		0	0	3+	3+	0	0	±	±	±	±	Diabetes well controlled by diet from 1918-1926.	
7	62	F.	Stout	19	12	30			120	90	125	80		0	+	2+	2+	0	0	0	0	0	0	Carcinoma of colon, 1933.	
8	64	M.	Stout	17	12	20	110	70	110	80	130	80	+	+	3+	0	4+	0	0	0	0	0	0	Coronary occlusion, 1936.	
9	69	M.	Stout	14	9	60			120	80	125	80		0	3+	0	2+	0	0	0	0	0	0		

showed the least disturbance, Case 6, had no calcification. Three of the patients, one man and two women, developed cardiac infarction.

### CORONARY OCCLUSION

In the three groups of this series, seven of the patients had coronary occlusion; two of these died after these observations were made. Of the patients studied in 1924 and 1927, who could be followed, 10 were believed to have died of cardiac infarction. On reviewing their case histories together with those of the seven instances of infarction in the present series, it was found that seven patients had no calcification of the arteries of the lower extremities and six had hypertension. The outstanding characteristic of this group was stoutness which was present in 15 of the 17 patients. In this small number of patients it appears that the absence of atherosclerosis in the lower extremities as determined by the methods used in this investigation does not offer any assurance that the patient will not develop occlusion of the coronary arteries. Also it seems that good control of the diabetes is more effective in the prevention of circulatory disturbances of the lower extremities than in the reduction of the incidence of cardiac infarction.

### THE RELATIONSHIP OF ABNORMAL CHOLESTEROL METABOLISM OR A HIGH FAT DIET TO ATHEROSCLEROSIS

It is not our intention here to enter into any wide discussion of this controversial subject. Critical clinicians and competent experimental pathologists such as Wilder,<sup>3</sup> Duff,<sup>4</sup> Joslin,<sup>5</sup> Leary<sup>6</sup> and Weiss and Minot<sup>7</sup> have presented divergent yet cogent arguments either in favor of or against the view that atherosclerosis in the diabetic is caused by an abnormal cholesterol metabolism or a high fat diet. Newburgh,<sup>8</sup> who has always treated his patients with a high fat diet, does not believe that the incidence of vascular disease is inordinately high in his clinic. This question, it would appear, cannot be settled until a different approach can be made to the study of the development of human atherosclerosis.

### SUMMARY AND CONCLUSIONS

The vascular status of 52 diabetic patients who have been under observation for a period of 10 to 13 years forms the basis of this report.

The patients were divided into three groups: Group I, those who had *excellent* or *good* care throughout most of their diabetic life; Group II, those who were regarded as uncoöperative; Group III, those who passed through the pre-insulin treatment but who had been undernourished as a result of a low caloric diet or of very severe diabetes, but who had been well controlled since insulin.

Of the patients in all groups, 23 had systolic blood pressures that were 150 mm. or more. Only six of these had diastolic blood pressures that exceeded 100. Five had systolic blood pressures that were more than 200 mm.

It was observed during this period—10 to 13 years—that there was no inordinate rise of the systolic or diastolic blood pressures in either the co-operative or uncoöperative groups. Thirty-two of the 47 patients upon whom we had blood pressure readings over a 10 year period had no essential change in their blood pressures. There was no correlation between the height of the blood pressure and the impairment of the circulation of the lower extremities.

We believe that the data presented offer further proof that atherosclerosis of the lower extremities can be prevented or delayed by controlling the diabetes continuously provided the control is started early enough after the inception of the disease. Under the conditions of this study a diet which was moderately high in fat did not produce atherosclerosis of the lower extremities provided the diabetes was kept under control. An increase of body weight appeared to favor atherosclerosis of the lower extremities but since in most instances this was associated with poor control of the diabetes it is impossible to appraise the effect of stoutness.

In the small series of patients with occlusion of the coronary arteries there was no relationship of this complication to the degree of atherosclerosis of the lower extremities as demonstrated by the methods used. It appeared that good control of the diabetes was a more influential factor in the prevention of circulatory impairment of the lower extremities than in the prevention of cardiac infarction. Coronary occlusion seemed to be favored by stoutness which was present in 15 of the 17 patients.

Eleven of the patients showed a lack of parallelism between calcification of the arteries of the lower extremities and the state of the circulation. Clinical signs of circulatory deficiency must be regarded as strong presumptive evidence of impaired circulation. Therefore it appears that the demonstration of calcification of the arteries can only be regarded as accessory evidence of atherosclerosis which may be assumed if a patient has had uncontrolled diabetes for a period. Five of our patients have had calcification of the arteries of the lower extremities for 13 years.

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# OBSERVATIONS ON THE USE OF FLUIDS AND LUMBAR PUNCTURE IN THE TREATMENT OF DELIRIUM TREMENS \*

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IN 1915 Steinebach,<sup>1</sup> reported that he observed remarkable improvement in 18 cases of delirium tremens immediately after lumbar puncture and withdrawal of cerebrospinal fluid. He thought that improvement resulted from the reduction of a high cerebrospinal pressure and a diminution of "toxic" elements circulating in the cerebrospinal fluid. Since Steinebach's first report appeared, the literature pertaining to the treatment of delirium tremens has contained other citations of the therapeutic efficacy of lumbar puncture in the treatment of this disorder (Hoppe,<sup>2</sup> Goldsmith,<sup>3</sup> and Ebaugh and Johnson<sup>4</sup>).

Assuming that an increase in cerebrospinal fluid pressure and edema play a significant rôle in the pathogenesis of delirium tremens, Cline and Coleman,<sup>5</sup> and Piker and Cohn,<sup>6</sup> have treated patients suffering from delirium tremens by attempting to bring about cerebral dehydration through direct and indirect means. The routine procedure of these investigators (Jr. Am. Med. Assoc., August 6, 1936 and January 3, 1937) includes the withdrawal of large quantities of cerebrospinal fluid, intravenous administration of 50 c.c. to 100 c.c. of a 50 per cent solution of dextrose, massive oral doses of magnesium sulphate and a limitation of fluid intake for the first 24 hours after admission. Improvement following this program of treatment is attributed to cerebral dehydration.

That an intravenous hypertonic solution of dextrose is productive of a significant reduction of increased cerebrospinal fluid pressure is doubtful. The immediate decrease in cerebrospinal fluid pressure which occurs after administration of an intravenous hypertonic solution of dextrose is followed within a few hours by a rise which is sometimes higher than the original level (Milles and Hurwitz,<sup>7</sup> Masserman,<sup>8</sup> Jackson et al.,<sup>9</sup> Lindemulder,<sup>10</sup> and Haug.<sup>11</sup>

It is common knowledge that the majority of delirium tremens patients give a history of having eaten inadequately before the onset of their delirium. During the delirium many patients perspire freely and show evidence of a general intoxication. These factors raise a question concerning the rationale of instituting intensive dehydrating measures in the treatment of uncomplicated cases of delirium tremens. Some patients appear to be dehydrated at the time of their admission to the hospital.

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The observations reported in this paper were made at the Boston Psychopathic Hospital Director C. Macfie Campbell.

This paper presents the results obtained in the treatment of 40 cases of delirium tremens. Twenty of the group had a lumbar puncture and were restricted in their intake of fluids. Twenty did not have a lumbar puncture and were given large quantities of fluids.

### MATERIAL AND PROCEDURE

The 40 patients used in this study were men between the ages of 25 and 49 years, who were admitted to the Boston Psychopathic Hospital in 1936 and 1937. All gave a history of years of excessive drinking which was increased in amount shortly before the onset of the delirium. Upon arrival at the hospital they exhibited confusion, disorientation, visual and sometimes auditory hallucinations.

In view of the plan to give some of the patients large quantities of fluids, care was exerted to exclude from the group patients who were suspected of having intracranial conditions that are known to increase the cerebrospinal fluid pressure. Six patients had mild respiratory infections. The others were free from pulmonary complications and gross clinical evidence of liver pathology, such as jaundice and palpable hepatic enlargement. Edema was not observed in any of the cases.

No patient was permitted to have alcoholic drinks during his stay in the hospital. Immediately after admission alternate cases of the group were given an oral dose of paraldehyde sufficiently large to induce sleep. While the patient was sleeping, 10 to 40 cubic centimeters of cerebrospinal fluid were removed by means of a lumbar puncture. This procedure was followed by intravenous administration of 100 c.c. of a 50 per cent solution of dextrose. As soon as the patient awakened he was given one ounce of magnesium sulphate by mouth. Then he was allowed to have a high caloric diet rich in vitamin B and fluids amounting to 1000 c.c. for the first 24 hours. Thereafter fluids were given as the patient desired them.

The patients of the second group did not have a lumbar puncture and were not restricted in their intake of fluids. On the contrary, they were given 1500 to 2000 c.c. of a 5 per cent solution of dextrose in normal saline by hyperdromoclysis soon after admission. Later they received a high caloric diet rich in vitamin B and were urged to drink large quantities of milk, fruit juices and water. In some instances they drank as much as 2000 to 3000 c.c. of liquids within a period of 24 hours. Excitement and restlessness were controlled by oral doses of paraldehyde.

### RESULTS AND COMMENTS

All patients of both groups recovered from their delirium within one to three days after admission. However, the patients who were not restricted in the intake of fluids and did not have a lumbar puncture showed less tremulousness and fewer signs of exhaustion after the acute features of their mental disorder subsided than those patients who were treated by the lumbar

puncture and dehydrating measures. Several patients of the latter group, whom we could not keep in bed the usual length of time after the lumbar puncture, suffered from headache.

At first glance, it might seem paradoxical that in the treatment of delirium tremens two seemingly opposed procedures should induce almost equal beneficial results. Careful scrutiny of the two technics discloses, however, that both have several significant factors in common. All patients of both groups ceased drinking immediately after admission. All patients received a high caloric diet rich in vitamin B. Likewise, all patients obtained rest and sleep. It is our opinion that these factors, particularly food and sleep, played a greater rôle in recovery than might be ascribed to the effects of withdrawal of cerebrospinal fluid.

Because of reasons obvious to those who have treated excited delirium tremens patients, we were able to obtain reliable cerebrospinal fluid pressure readings in only 12 cases. All were normal. The figure is too small to enable one to draw accurate conclusions with regard to cerebrospinal fluid pressure in delirium tremens. It is significant, however, in the light of the popular belief that an increase of cerebrospinal fluid pressure exerts a conspicuous influence in the pathogenesis of this disorder.

The failure to observe an increase of cerebrospinal fluid pressure in our cases might be explained by the fact that an effort was made to exclude from the group all patients suspected of having complications which are known to initiate an increase of pressure.

### CONCLUSIONS

1. Lumbar puncture is of great diagnostic significance in delirium tremens but our observations indicate that it is not an important factor in the treatment of this disorder.

2. In the absence of intracranial complications which are known to initiate an increase of cerebrospinal pressure, it seems wiser to give delirium tremens patients large quantities of fluids than to restrict their intake of fluids.

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# ADVANTAGES OF PROZINSULIN\* (PROTAMINE ZINC INSULIN) THERAPY: DIETARY SUGGESTIONS AND NOTES ON THE MANAGEMENT OF CASES

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Prozinsulin is being used in the routine control of the diabetic state. Difficulties have been encountered in a certain group of patients with this type of therapy. This group corresponds in part to the same group who had their difficulties with the old insulin. The purpose of this paper is to present a method, applicable in particular to the control of the unstable case. In addition, it is felt that the regime can be used with advantage in treating other diabetic patients. The successful change to Prozinsulin is dependent upon a complete rearrangement of the diet.

The physiological necessity for these suggested changes can be stated briefly.

1. Prozinsulin differs from old insulin in its delayed absorption and prolonged activity.
2. It is essential that maximal carbohydrate availability coincide with maximal insulin activity.
3. Slowly absorbed carbohydrates must be used to compensate for the delayed absorption of Prozinsulin.
4. The continuous action of Prozinsulin from supper to breakfast requires a dietary arrangement which will prevent nocturnal hypoglycemia.

The attempt to satisfy these requirements resulted in two principal changes.

1. Distribution of the amount and kind of carbohydrate, in relationship to the diurnal variations of glycosuria.
2. Insistence upon the consumption of about 30 grams of protein (150 grams of meat), or its equivalent at the evening meal.

A maximum amount of carbohydrate can be metabolized by any diabetic patient when it is distributed evenly throughout the day. When apportioned into the three customary feedings, this maximum cannot be utilized completely, and postprandial glycosuria may occur. The explanation for this lies in the fact that only so much glucose can be utilized per unit of time, and therefore, when more is presented at any one time than can be disposed of immediately, the surplus induces hyperglycemia with resultant glycosuria. In normal individuals, the self-regulating mechanisms are sufficiently elastic

\* "Prozinsulin" is offered as a convenient contraction of "Protamine Zinc Insulin."

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to cope with the extreme variations of the average daily diet. The diabetic who has his insulin injected periodically, however, is limited in his diet to the predetermined COH-to-insulin ratio. Since Prozinsulin is designed to work over a long period of time, it is necessary that the COH capacity be not exceeded at any one time.

The actual amount of Prozinsulin required by any individual patient is largely a matter of trial and error. When the patient has been using old insulin, it is fairly simple to estimate the initial trial dose. This is usually two-thirds of the total daily dosage of the old insulin, given once daily, before breakfast. For the first three to seven days, supplementary doses of old insulin must be administered at breakfast and lunch-time, in five or ten unit doses. Depending upon the time and amount of glycosuria, the injections of regular insulin are stopped, first at one meal, then at both. The amount of Prozinsulin is determined by the prebreakfast urine specimen. It can be increased at three-day intervals by five-unit doses, until the morning urine specimen is sugar-free.

The patient is given a diet with the following composition: carbohydrate 150 grams, protein 80 to 100 grams, and fat in amounts required to bring the caloric intake up to the desired level. The total amount of carbohydrate is divided as follows: one-fifth for breakfast and two-fifths each for lunch and supper. The protein is divided to allow one-sixth at breakfast, and one-sixth or one-third at lunch, and two-thirds or one-half at supper. The Prozinsulin dosage is increased or decreased depending upon the morning findings in the patient's urine. When the morning urine no longer contains sugar, then changes are made in the diet arrangement to suit the conditions present. Frequently glycosuria after lunch and supper persists even though the morning urine is sugar-free. To increase the dose of Prozinsulin at this time is definitely contraindicated. The first point of attack is the post-lunch glycosuria, for, when it is eliminated, the evening glycosuria will tend to disappear spontaneously. Elimination of rapidly absorbed fruits and fruit juices, and the substitution of their glucose value by other forms of COH, is the first procedure towards solving the difficulty of post-lunch glycosuria. If this is not successful, then the shifting of five to ten grams of COH from lunch to supper should eliminate this difficulty. It is essential to spread the time of the meals throughout as much of the day as possible, in order to allow for the complete utilization of one meal before overloading with the next. In addition, this procedure will reduce the time interval between supper and breakfast. It is a common experience that hospitalized patients whose meals are served at eight A.M., eleven-thirty A.M., and four-thirty P.M., will be difficult to control with Prozinsulin. This concentration of the food within an eight hour period leads to glycosuria. The sixteen hour fasting period from supper to breakfast invites frequent hypoglycemic shocks. These very same patients, when ambulatory and treated in the diabetic clinic, present no such difficulties, in that the spacing of meals is not dependent upon such rigid hospital routine.

When the patient consumes one-half to two-thirds of the daily protein allowance at supper time, it is rare to find nocturnal hypoglycemic episodes, the reason for this being that about one-half of the protein consumed is converted into available carbohydrate. This conversion is slow. Meat is not emptied from the stomach very rapidly, and may take up to three hours.

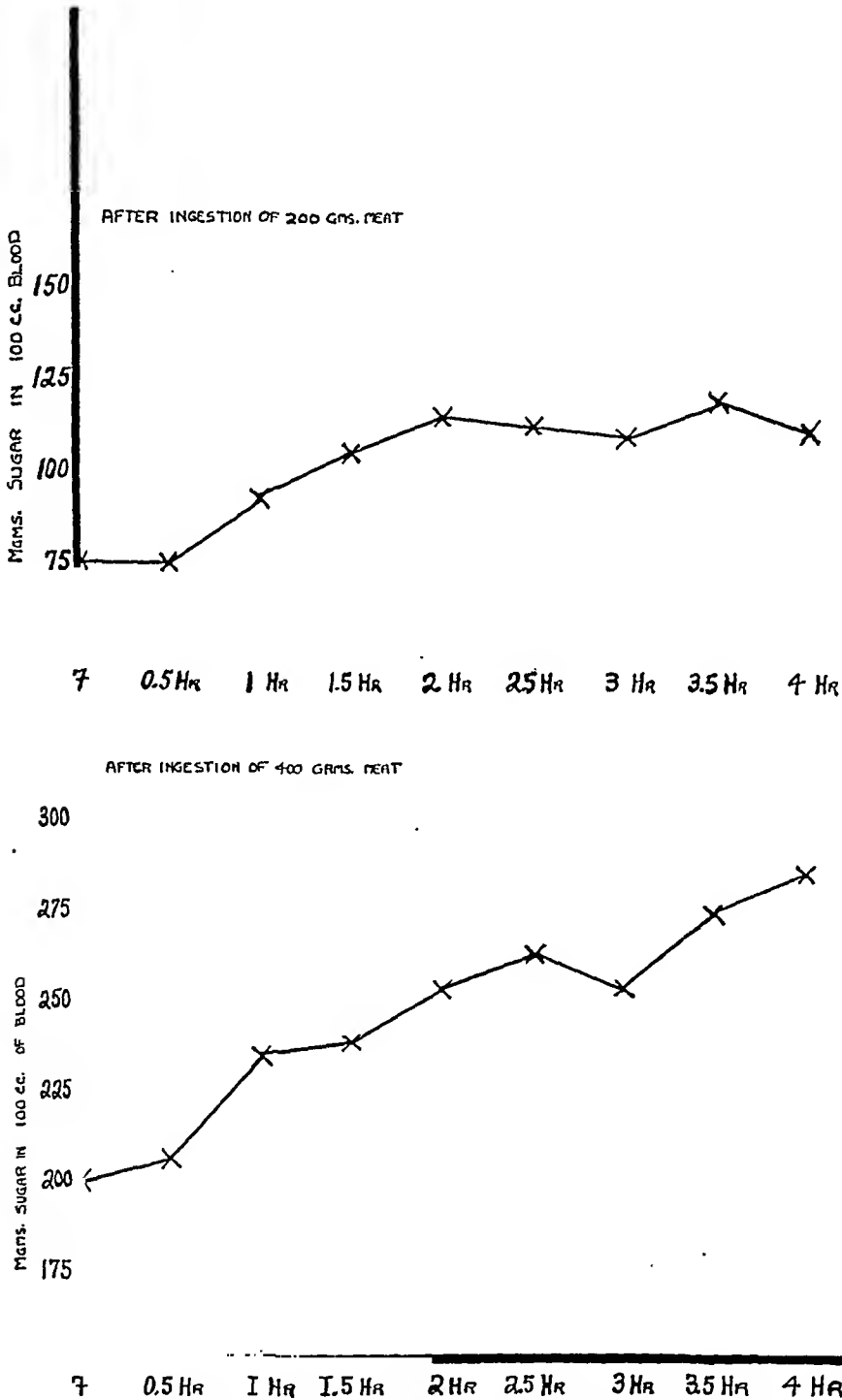


FIG. 1. The effects upon the blood sugar level of the ingestion of meat: (a) 200 gm. of meat, (b) 400 gm. of meat.

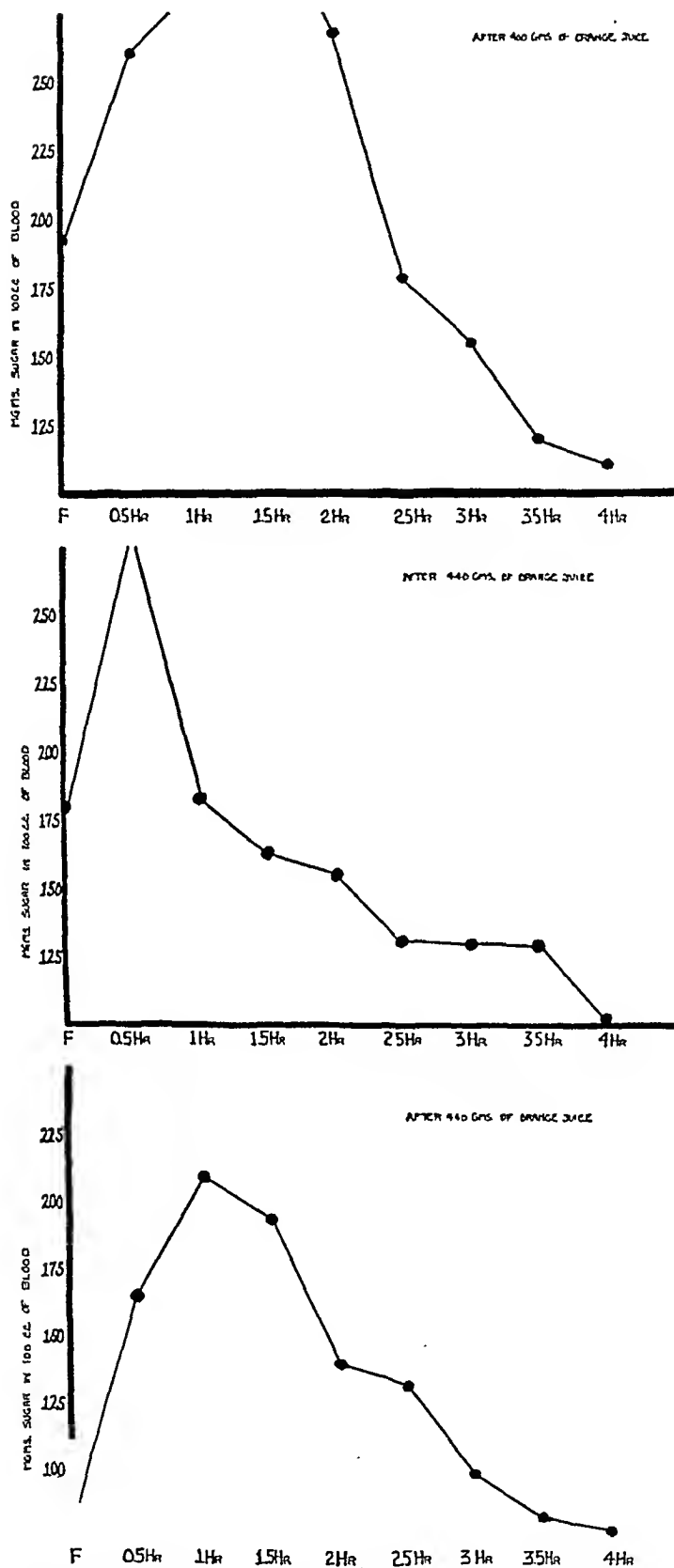


FIG. 2. Three blood sugar curves (a, b, c) illustrating the effect of the ingestion of 400-440 gm. of orange juice.



Then the small intestinal digestion of the meat occurs, consuming more time. The absorption of the amino acids, the de-aminization, the subsequent synthesis of the fragments to glucose, all require time. The net result is that there is prolonged availability of carbohydrate derived from the meat for six to eight hours. Experimentally, this has been shown by Conn and Newburg, and confirmed by us (figure 1, *a* and *b*). These curves represent blood sugar changes at half-hourly intervals following the ingestion of meat. No Prozinsulin was given for 24 hours preceding the test. This was done to avoid masking the slow blood sugar rise. These are examples of many similar determinations on a series of patients. These experiments were done under identically the same conditions as the orange juice experiments (see figures 2*a*, 2*b*, 2*c*). Contrast figure 1*b* with figure 2*b*. The carbohydrate equivalents were the same. The slow rise in blood sugar concentration, and the absence of any tendency to rapid fluctuations after the ingestion of meat, establishes its usefulness without question.

Some patients will require the addition of even more meat at supper and the setting of the time as late as seven-thirty to eight P.M. It is only the rare patient who actually requires a midnight feeding. Certain patients, however, request the privilege of indulging in a midnight "snack." With old insulin, this was a disturbing departure from the routine, and often necessitated an extra insulin injection at such times. With Prozinsulin, no special difficulty is encountered in allowing such liberty, provided the principle of avoiding rapidly absorbable COH is observed. Reserving part of the protein and COH from the evening meal furnishes a meat sandwich or hamburger for the midnight feeding, without causing marked fluctuations in the blood-sugar level. Prozinsulin is being used to simplify life for the diabetic, and not to complicate it. The use of multimeal schedules beyond the conventional three is an unnecessary complication.

With Prozinsulin, the commonest time for glycosuria is after breakfast. This is a natural sequence to the particular properties of Prozinsulin. The breakfast and the postbreakfast periods represent the time of minimal insulin availability. It is the period of waning activity of the previous morning's injection. The maximum availability of the current injection, by virtue of its slow absorption, does not become manifest until close to lunch time. Therefore, it is essential to prescribe the use of small breakfasts, and to eliminate rapidly absorbable fruits and fruit juices from that meal. When old insulin was administered, it was the practice to order the major fraction of the daily allowance of insulin before breakfast. Because of its rapid action, it necessitated the consumption of large breakfasts. In addition, fruits or fruit juices were a practical necessity to prevent hypoglycemia during the time before the major part of the breakfast was made available. In this series of 140 patients, very few now require the use of a single supplementary dose of regular insulin. Each patient gets along on a single dose of Prozinsulin every morning before breakfast. If postbreakfast glycosuria persists, then generally the subtraction of a few grams of COH from the

meal, as described above, eliminates this difficulty. Should hypoglycemic episodes occur consistently after any one meal, then the addition of a few grams of carbohydrate and protein to that meal is indicated. Difficulties will be encountered during the transition phase, but by the use of diet shifts these can be corrected. When the early morning urine is free of sugar the Prozinsulin dosage should not be increased without compensating by increasing the protein allowance at supper; even then, other methods should be tried first.

The hypoglycemic episodes which occur during the middle of the night and early in the morning are quite different from those which occur during the middle of the day. The nocturnal episodes, as explained above, are due to the action of the Prozinsulin long beyond the availability of the supper meal to buffer it. The daytime hypoglycemic episodes are seen more frequently in those patients having temporary postprandial glycosurias.

Figures 2, *a*, *b*, and *c*, illustrate the blood sugar curves of patients who had been given 400 grams of orange juice on a fasting stomach, 24 hours after the last dose of Prozinsulin. The rapid rise of the blood sugar level within one-half to one hour, and the subsequent drop to hypoglycemic levels are noteworthy. Attention should be drawn to this rapidity of the rise and fall of the blood sugar concentration. It is this precipitous drop in blood sugar concentration which initiates the subjective symptoms associated with hypoglycemia. During these tests, it was not uncommon for patients to evince symptoms of "mild shock" during the third and fourth hours. This is an illustration of the production of hypoglycemia by induced hyperglycemia; a phenomenon which is frequently observed when studying the glucose tolerance of normal people. Its occurrence in the diabetic using Prozinsulin is of more than theoretical interest, in that this mechanism can be responsible for daytime hypoglycemia. Diabetic patients using the old insulin did not show this phenomenon. As illustrated, the use of Prozinsulin brings about a sufficient restoration of COH utilization to exhibit this phenomenon, and at times even in an exaggerated form. Eliminating postprandial hyperglycemia and glycosuria practically automatically eliminates this type of hypoglycemic shock. When between meal feedings are desirable for other reasons, such as satisfying the hunger of a growing child in the mid-afternoon, then a food mixture, such as crackers and milk, or bananas and cream, is preferable to fruit or fruit juice alone. The carbohydrate of orange juice, being practically pure glucose, is rapidly absorbed and immediately available. The more complex types of carbohydrate behave differently, by virtue of the fact that the preliminary processing of digestion must take place before the monosaccharide becomes available. In addition, another method of achieving delayed availability presented itself in a method of prolonging gastric-emptying time by taking advantage of the well known effect of fats. Figures 3*a* and 3*b* illustrate the blood sugar variations in the same patients after the ingestion of the ripe whole banana, with and without cream. The effect of the addition of the cream is quite obvious. The peak rise in blood sugar

concentration is delayed until the second hour or later. The rate of rise is slower. The peak blood sugar concentration is at a lower level. The fluctuations are not as violent as without the cream. These curves were obtained 24 hours after Prozinsulin. As stated previously, the activity of the Prozinsulin becomes manifest after the second hour following the injection.

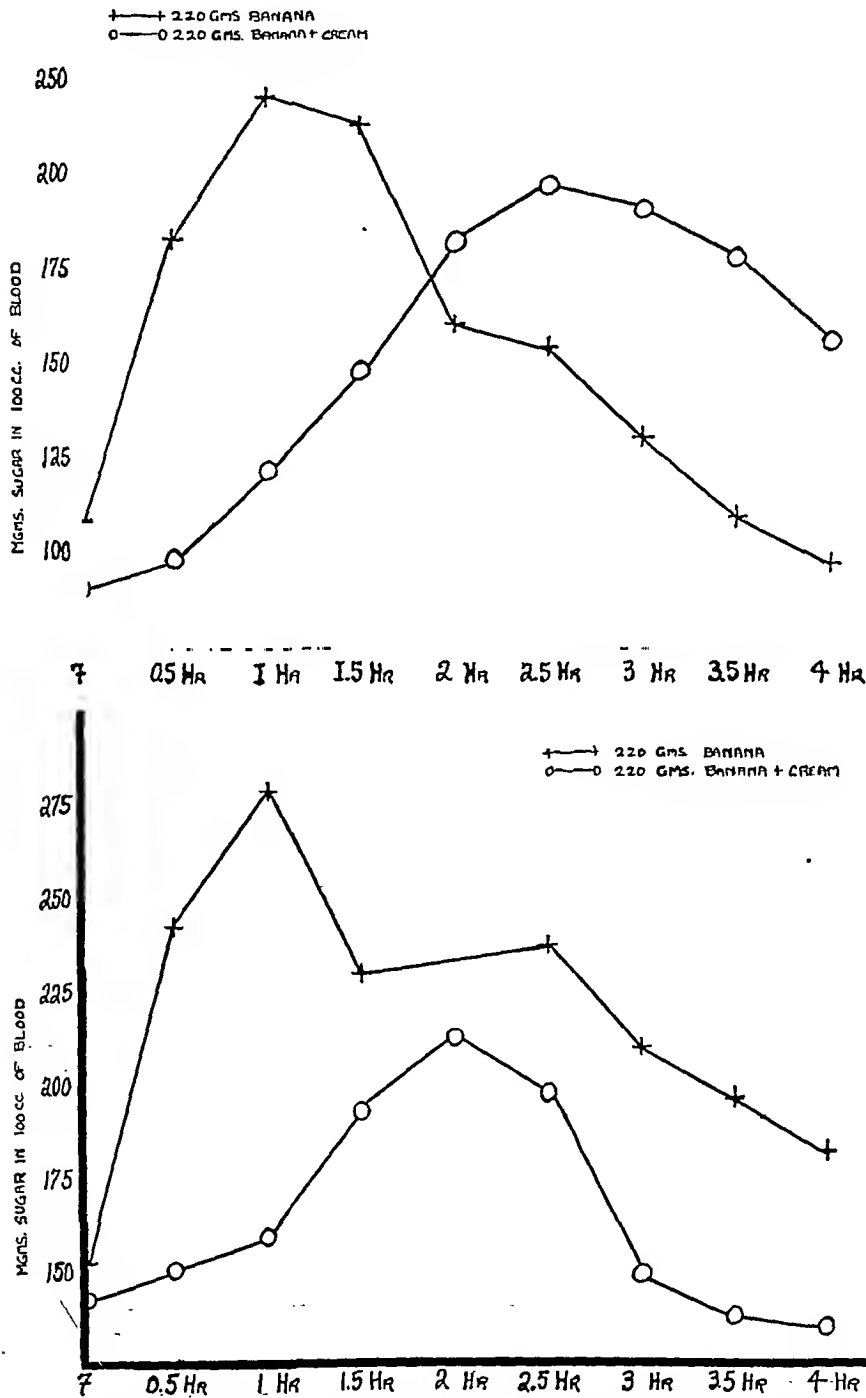


FIG. 3. Blood sugar curves in two patients (a, b) showing in each the effect of ingesting banana (220 gm.) alone and of ingesting the same amount of banana with cream.

Therefore, the use of cream with the breakfast fruit delays its availability sufficiently to bring it within the time of the beginning insulin activity of the prebreakfast injection. Experimental data are being collected as to the rate of availability of various foods and food mixtures, but the problem is so extensive that considerable investigation will be required.

A word of caution must be given to patients using Prozinsulin before indulging in unusual or very active exercise. This is one condition which must be met by extra feeding at the time of the activity, generally bread and butter. Swimming, because of the danger to life in case of hypoglycemic reaction, should always be preceded by food. One intelligent college student using Prozinsulin has determined his tolerance for golf by his score. He noticed a consistent incoördination in addressing the ball on the fourteenth tee. A bottle of popular sweet drink became standard in his golf bag, and now at the thirteenth green he drinks half of it, and has been able to compete successfully in tournaments. Another danger is skipping meals. This means that patients taking Prozinsulin cannot take the luxury of sleeping late on Sunday or any other morning, without encountering hypoglycemic episodes and their attendant dangers. Should the patient know that he is going to sleep late any one morning and skip breakfast, then he should prepare himself for it. This can be done, for example, as follows. On Saturday morning, if the patient uses over 20 units daily, he should decrease the amount of the injected Prozinsulin about 20 per cent. Late Saturday night, before going to bed, one-half of the usual Sunday morning breakfast should be consumed. With this protection, it is safe to allow the patient to sleep until his noon meal. This practice of Sunday morning breakfast-lunch is a potential danger to patients using Prozinsulin, and must be explained in detail to them.

Insofar as the technic of the actual injection of Prozinsulin goes, little need be added to what has already been described. One additional factor of safety in preventing local skin reactions has been the instruction to the patients to use five-eighths inch to three-fourths inch 25 gauge needles, and to inject as deeply as possible. It is essential to avoid intradermal injections. No detectable difference in activity exists between the U-40 and the U-80. It is preferable to inject as small a volume as is consistent with accurate measurements.

There seems to be no question about the superiority of Prozinsulin over old insulin for routine care of patients. Certainly transient and severe ketosis is less common in patients using Prozinsulin.

Table 1 summarizes the incidence of ketonuria in a group of patients before, and after the introduction of Prozinsulin in 1936. The contrast is striking and needs no further explanation.

When old insulin was used, the appearance of glycosuria was frequently associated with ketonuria. This was a result of the intermittent oxidation of carbohydrate, due to the intermittency of insulin availability. Ketonuria was especially noted in the early morning, the greatest interval of time after

TABLE I

## Incidence of Ketosis in Selected Patients

Patients	1931		1932		1933		1934		1935		1936		1937	
	Total Number of Visits	Number of Visits with Ketonuria	Total Number of Visits	Number of Visits with Ketonuria	Total Number of Visits	Number of Visits with Ketonuria	Total Number of Visits	Number of Visits with Ketonuria	Total Number of Visits	Number of Visits with Ketonuria	Total Number of Visits	Number of Visits with Ketonuria	Total Number of Visits	Number of Visits with Ketonuria
J. F. ....	8	5	15	13	11	8	12	10	12	9	12	0	12	0
A. J. ....	30	12	40	6	20	4	16	7	14	2	40	0	40	0
G. K. ....	20	9	10	2	15	2					12	0	12	0
S. M. ....	9	1	12	2	10	2	12	0	12	0	12	0	12	0
M. J. ....	12	4	11	1	10	4	20	2			12	0	12	0
M. B. ....							16	3	14	1	35	0	35	0

the last insulin injection. Episodes of interval glycosuria may still be seen in patients using Prozinsulin, but, in spite of glycosuria of up to 10 per cent, ketosis has never been present. Because of the prolonged activity of Prozinsulin (over 24 hours) there is never any time in the course of a day when insulin is not acting. This fact is one of the strongest arguments for the use of Prozinsulin. So much so, that now it is routine to use Prozinsulin both pre- and post-operatively. In the past, patients frequently had a period of ketosis after general anesthesia, but with Prozinsulin, this can be prevented. No attempt is made to control the glycosuria completely with Prozinsulin alone. Supplementary doses of old insulin are used for that purpose. Dosage of the latter is determined by the fractional urine specimens. More satisfactory control can be achieved this way, and ketosis certainly avoided. Too much stress cannot be laid upon the necessity for complete coöperation between the surgeon and the physician, when using this therapy; properly handled, it offers definite advantages; improperly handled, it is a menace. The utmost vigilance by a properly trained nursing and house staff is required.

Time is an important factor in the treatment of diabetic coma. Old insulin is still of paramount importance in this emergency. However, there is a definite place for Prozinsulin as a supplementary agent in coma therapy. Its continuous action helps bridge the gaps between the injections of old insulin. It prevents the tendency to ketone formation in those intervals when the activity of the one injection is spent, before the next injection is given.

One of the most important contra-indications to Prozinsulin is the presence of coronary artery disease. It is felt that the complete control of the glycemia as afforded by Prozinsulin is not tolerated by the older age group

with coronary artery disease, as evidenced by increasing anginal episodes. However, if one uses Prozinsulin in comparatively small doses to prevent excessive glycosuria and ketosis, without attempting too strict a control of the diabetes, it will be tolerated. Extreme caution must be used in transferring a patient of this type from the old insulin to Prozinsulin.

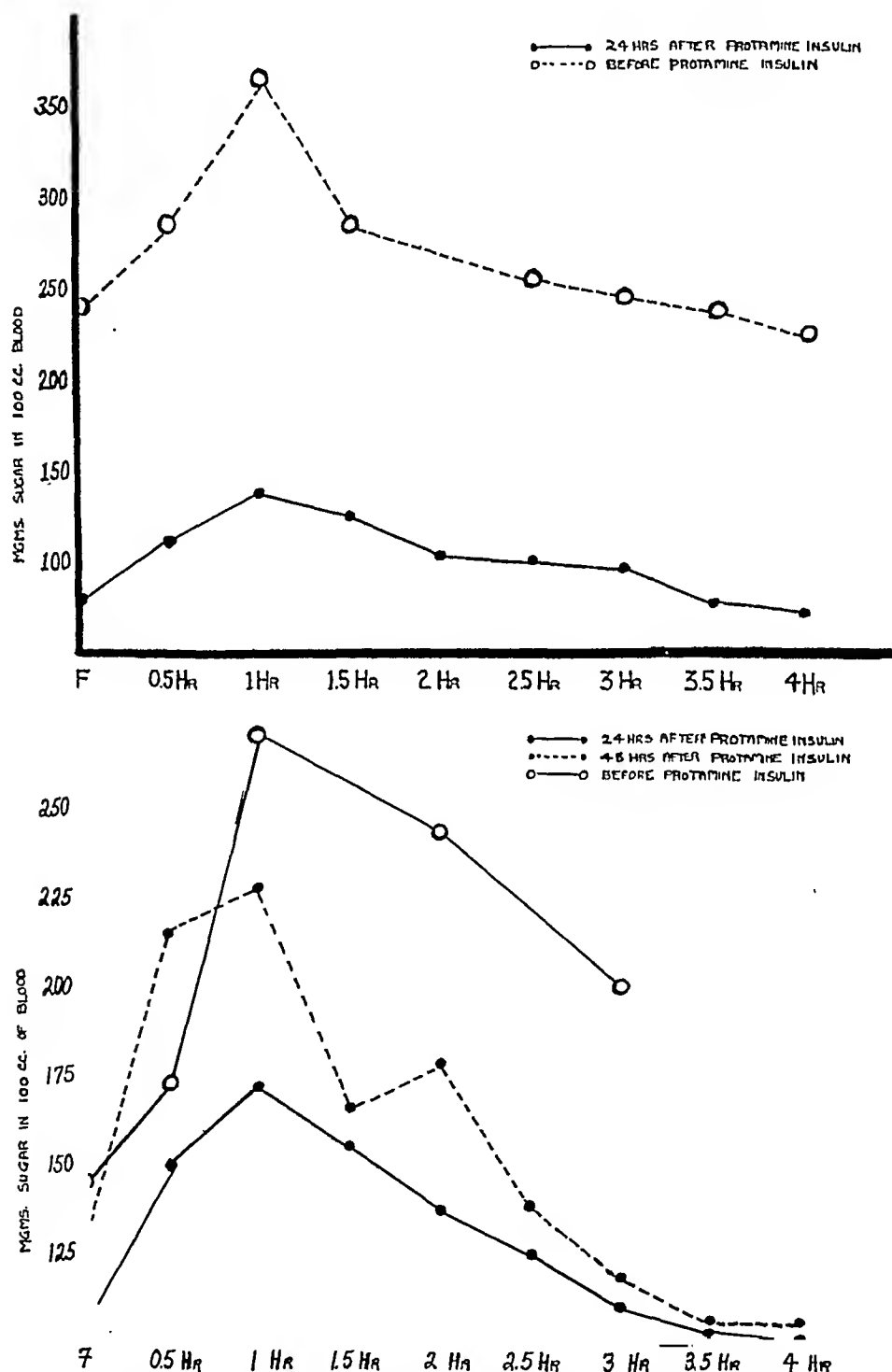


FIG. 4. Glucose tolerance curves obtained before the administration of protamine insulin and at varying intervals (24, 48 hours) after a dose of protamine insulin.

On the other hand, mild diabetics who require little or no insulin, do much better with small daily doses of Prozinsulin. The experimental data illustrated (figure 4) reveal a practically normal utilization of carbohydrate 24 hours after the injection. When no insulin is given for several days, there is a typical diabetic type of response to the test meal. If the normal glucose tolerance curve is of any significance as indicating a return to normal carbohydrate metabolism, then one can anticipate arrest, amelioration or prevention of the degenerative changes usually seen in this group of patients.

The age distribution of the patients using Prozinsulin in this clinic is given in table 2. It illustrates the general age variations in the clinic.

TABLE II

Age	Number of Cases	Age	Number of Cases
15-20.....	20	51-55.....	23
21-25.....	8	56-60.....	13
26-30.....	9	61-65.....	9
31-35.....	6	66-70.....	7
36-40.....	0	71-75.....	2
41-45.....	17		
46-50.....	16		

The patients in the older age group using this preparation are mild cases, requiring doses of 20 units or less daily. As stated previously, it is not good practice to use Prozinsulin in the severe, unstable, elderly patient, when the possibility of hypoglycemic episodes exists.

The efficiency of this insulin preparation is undoubtedly greater than that of the old insulin. Where conditions are constant, that is, diet, rate of growth, etc., the saving amounted to from 5 to 40 units daily. However, the tendency in the adolescents has been to require increased amounts as they grow in height and weight, and as the diet needs increase.

#### SUMMARY AND CONCLUSIONS

With proper dietary control, Prozinsulin offers definite advantages for the routine care of diabetic patients. These advantages can be stated briefly as follows:

1. The single injection daily for patients.
2. Complete elimination of transient ketonuria.
3. Closer approximation to the normal carbohydrate metabolism.
4. Decrease in the incidence of hypoglycemic episodes.
5. Valuable as a supplementary agent in coma therapy.
6. Improvement in post-operative control of diabetic patients.
7. Obviates the absolute necessity of multi-feeding schedules, yet permits optional midnight "snacks."

The essentials of the suggested dietary regimes are as follows:

1. The use of small breakfasts.
2. Division of carbohydrate into  $1/5$ ,  $2/5$ ,  $2/5$  for the respective morning, midday and evening meals.
3. Distribution of protein to allow for over one-half of the daily allowance at the evening meal.
4. Increased time interval between meals with particular reference to late suppers.
5. Elimination from the diet of rapidly available carbohydrate.
6. Specific use of fats in delaying gastric-emptying-time, such as cream with banana.

The majority of patients respond well, and are controlled with greater ease on such a regime. Frequent observation and meticulous attention to details of diet will be rewarded by better control of even the most unstable cases. The use of supplementary doses of old insulin can be almost completely avoided.

We express our indebtedness to Eli Lilly & Company, and to E. R. Squibb & Sons, for their generous contributions of Protamine Zinc Insulin.



# CASE REPORTS

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## SPASM OF THE SPHINCTER OF ODDI; REPORT OF A CASE\*

By ISIDORE FEDER, M.D., *Brooklyn, N. Y.*

THE sphincter of Oddi (*sphincter choledochus*) serves an important function in the regulation of the normal flow of bile from the liver into the duodenum. Recent clinical and laboratory studies have emphasized the rôle that the sphincter plays in causing pain when its normal function is disturbed. Spasm of the sphincter may produce sudden obstruction of the choledochus with a marked increase in intraductal pressure. This condition may be responsible for the initiation of attacks of severe biliary colic. Such a case is herein reported. The relevant literature is briefly reviewed.

Schwiegler and Boyden<sup>1, 2</sup> have shown by their fine anatomical studies that the *sphincter choledochus* is a special constricting mechanism which develops at the site of junction of the common bile duct with the ampulla of Vater. The sphincter in its development is carried away from the intestinal muscle and set up as an independent mechanism for regulating the flow of bile.

Authorities differ somewhat as to the innervation of the sphincter. Doyon<sup>3</sup> states that the vagus contains motor fibers for the sphincter and inhibitory fibers for the gall-bladder. He observed that stimulation of the peripheral end of the splanchnic nerves caused simultaneously a contraction of the gall-bladder and an inhibition of the tonus of the sphincter. Ivy<sup>4</sup> feels that the vagi are the nerves predominantly concerned in increasing the resistance to the flow of bile into the duodenum and that spinal anesthesia decreases sphincteric resistance. Best and Hicken<sup>5</sup> state that the sphincter has an innervation derived from the sympathetic and parasympathetic systems and that it is as a rule in a contracted state under spinal anesthesia. Snell et al.<sup>6</sup> state that the splanchnic nerve carries sensory fibers from the bile ducts and that stimulation of this nerve causes contraction of the biliary sphincter.

The normal physiology and pharmacology of the sphincter deserve consideration. Meltzer<sup>7</sup> felt that the law of "contrary innervation" applied to the muscle fibers of the gall-bladder and the sphincter. During storage of bile in the gall-bladder the muscle fibers of the gall-bladder are inhibited and those of the sphincter are contracted. During discharge of bile into the duodenum the gall-bladder contracts and the sphincter relaxes. Ivy<sup>4, 8</sup> and Snell et al.<sup>6</sup> show that removal of the normal gall-bladder causes a temporary incompetence of the sphincter which later resumes its normal tone. Walters et al.,<sup>9, 10</sup> Colp and Doubilet,<sup>11</sup> Best and Hicken,<sup>5</sup> Snell et al.<sup>6</sup> and Ivy,<sup>4, 8</sup> by means of kymographic and choledochographic studies in the human and animal, have shown the following: Morphine and pilocarpine caused spasm of the sphincter of Oddi and an increase in intraductal pressure; nitroglycerine, amyl nitrite, atropine and intravenous bile salts relax the sphincter and decrease the resistance to the flow

\* Received for publication April 18, 1938.

of bile into the duodenum. Meltzer<sup>7</sup> found that concentrated magnesium sulfate solution instilled into the duodenum through a duodenal tube caused a complete relaxation of the contracted sphincter. This observation was confirmed by Lyon and Ivy.

Abnormal function of the sphincter, without gross or microscopic anatomical changes, may cause spasm of the sphincter. Ivy<sup>4</sup> finds that biliary dyskinesia or dyssynergia is caused by a disordered motor state of the sphincter of Oddi. Injection of cholecystokinin will stimulate the gall-bladder to contract and in the presence of a spastic sphincter will produce biliary colic. Weir and Snell<sup>12</sup> feel that persistent colic after removal of the gall-bladder may be the result of physiologic obstruction to the ductal system presumably due to spasm of the sphincter. Snell et al.<sup>6</sup> state that spasm of the sphincter occurs mostly in women many of whom have suffered from neurogenic visceromotor disturbances. Meltzer<sup>7</sup> observed that psychical influences and disorganized internal secretions which disturb the emotional equilibrium may produce a tonic contraction of the sphincter and thus cause not only biliary colic but jaundice.

The symptoms of spasm of the sphincter may not differ in any marked degree from those caused by calculus in the common duct. Snell et al.<sup>6</sup> find that the principal symptom is a frequent occurrence of severe colicky pain in the region of the gall-bladder. Nausea and vomiting may occur but chills, fever, leukocytosis and jaundice are absent. Major attacks may be interspersed with milder seizures of a similar character. Lipschutz<sup>13</sup> feels that cholecystography properly conducted is the most important single procedure in the diagnosis of dyskinesia. He shows that visualization of the biliary ducts is possible when there is spasm of the sphincter. To differentiate calculus from spasm biliary drainage is of value. The presence of cholesterol crystals will point to a diagnosis of calculus.

The treatment of spasm of the sphincter is primarily a medical problem. With the gall-bladder intact a diet is given containing fats, fruit juices and meat in order to excite the gall-bladder and relax the sphincter. Frequent duodenal drainage with instillation of 25 to 33 per cent magnesium sulfate may help relax the sphincter. The drugs which have been found to be of value are the nitrites, atropine, benzedrine and intravenous bile salts. Short wave diathermy in the right upper quadrant may afford some relief. Only temporary relief is obtained from cholecystectomy for the initial relaxation of the sphincter is soon followed by a resumption of the original tone and with it renewed attacks of biliary colic. Splanchnic nerve section has been found to be valueless. Dilatation of the sphincter through the common duct is only temporary in its effect. Colp and Doubilet<sup>14</sup> describe an instrument called the sphincterotome which safely divides the sphincter of Oddi through the common bile duct.

#### CASE REPORT

L. C., a female, 24 years of age, married, was admitted to the Beth-El Hospital on August 5, 1932. The present illness started one week prior to admission with fever, chills and malaise. There was a past history of attacks of biliary colic for 2½ years. These attacks had started shortly after delivery of her first child. Physical examination revealed rigidity of the neck, petechiae over the skin and enlargement of the spleen. A diagnosis of typhoid fever was made. All laboratory data confirmed this diagnosis. On August 20, in the fourth week of her illness, the temperature

which had begun to subside again rose and continued from then on with an intermittent character. The patient complained of severe pain in the right upper quadrant and subsequently a mass was noted in this region. The patient was operated upon September 14. An enormously distended perforated gall-bladder was found. It was completely enveloped by omentum. The gall-bladder wall at the liver site was completely destroyed and a large abscess cavity occupied the under surface of the liver. There was a calculus in the cystic duct. The gall-bladder was drained by tube and a cigarette drain was placed in Morrison's pouch. Culture of the gall-bladder pus showed the presence of *B. typhosus* and *Staphylococcus aureus*. Roentgen-ray examination showed elevation of the right cusp of the diaphragm and diminution of aeration at the base of the right lung due to the subphrenic inflammation. The temperature subsequently returned to normal. The biliary fistula continued to discharge bile and pus. The patient was discharged from the hospital November 12, 1932.

Drainage from the biliary fistula continued at home for about two months after which time the sinus tract healed. At this time the patient began to suffer attacks of biliary colic which were relieved by spontaneous opening of the sinus with a discharge of bile and pus. On May 30, 1933 the patient was admitted to the Brooklyn Jewish Hospital and reoperated upon. A thick walled, granular gall-bladder containing a bile pigment calculus, together with the fistulous tract was removed. The appendix also was removed at this time. Microscopic examination of the gall-bladder showed a fibrous, thickened serosa. The mucosa was ulcerated. The wall was infiltrated with an unusual number of plasma cells and eosinophiles. The pathological diagnosis was chronic ulcerative cholecystitis with cholelithiasis and fibrosed appendix. The patient made an uneventful recovery and was discharged June 11, 1933.

The patient felt well for about four months after her discharge from the hospital. In October 1933 she suffered a severe attack of biliary colic and from then until September 1935 had a number of these attacks with long intervals of apparently good health between the attacks.

In September 1935 an unusual sequence of symptoms began which is of the utmost interest. The patient began to have menstrual disturbances. Menstruation occurred irregularly every few weeks. Bleeding at times was only moderate and of short duration and at other times was rather profuse and lasted for 10 to 12 days. She gained about 20 pounds over a short period of time, the greatest distribution of fat being over the hips and thighs. Attacks of biliary colic began to occur more frequently. These attacks were preceded and followed by symptoms which had not existed heretofore. Previous to the onset of an attack the patient complained of extreme hunger which lasted for a few days. Then there occurred an attack of pain which started in the right upper quadrant and radiated to the back, right shoulder and arm. There was nausea but no vomiting. The height of the pain lasted a short while and was relieved either spontaneously or by morphine sulphate of which  $\frac{3}{4}$  of a grain had to be given at times. Nitroglycerine in a dose of  $\frac{1}{50}$  grain given hypodermically on a number of occasions was without effect. After the attack of colic subsided there was residual tenderness in the right upper quadrant and for a number of days tenderness along the entire course of the colon. There was then a more or less abrupt cessation of pain and tenderness, at which time the patient complained of generalized itching of the skin and an urticarial rash developed. At no time was icterus noted clinically nor was there an increased icterus index during or after the attack of pain.

In December 1935, in order to reduce her rapidly accumulating weight, the patient took a number of capsules of dinitrophenol over a short period of time. This was followed by hyperpyrexia and extreme jaundice. Upon cessation of medication and after administration of intravenous glucose solution the jaundice and fever subsided.

On February 16, 1937 the patient was readmitted to the Beth-El Hospital. Blood chemistry showed albumin 4.3 and globulin 2.4 grams per 100 c.c.; sugar 86, urea 11.5,

cholesterol 110 and cholesterol ester 54 milligrams per 100 c.c. A galactose tolerance test was done on February 19. The fasting blood sugar was 87; specimens taken at  $\frac{1}{2}$  hour intervals for two hours after the galactose showed 95, 93, 90 and 40 mg. of sugar per 100 c.c. A glucose tolerance test was repeated February 29. The fasting blood sugar was 72; specimens taken at  $\frac{1}{2}$  hour intervals after the glucose showed 95, 96, 93 and 90 mg. per 100 c.c. Specimens of urine taken at the same intervals during both of these tests showed no sugar. Microscopic examination of a specimen of bile obtained by drainage did not show cholesterol crystals. The blood count, gastric analysis and Wassermann tests were negative. The basal metabolic rate was minus 22. Roentgen-ray of the gall-bladder region showed a peculiar linear shadow density about  $\frac{3}{4}$  inch long in the right upper quadrant. Its cause could not be determined. Roentgen-ray of the sella turcica was negative.

In the light of the laboratory findings, the clinical symptoms were interpreted as follows: The patient was suffering from a glandular dyscrasia, in all probability hypopituitarism. This accounted for the low basal metabolic rate, the marked increase in tolerance to sugar, the gain in weight and the menstrual disturbances. Hypoglycemia was responsible for the hunger preceding the pain. The glandular imbalance led to spasm of the sphincter which initiated the attack of biliary colic.

The patient was discharged from the hospital on February 29, 1937. Glandular therapy with thyroid and pituitary extract was instituted. A rigid dietary regime was adhered to. Frequent biliary drainages were done. Short wave diathermy was given to the right upper quadrant. Despite intensive treatment the patient continued to have more frequent and very severe attacks of biliary colic. Surgical intervention was decided upon.

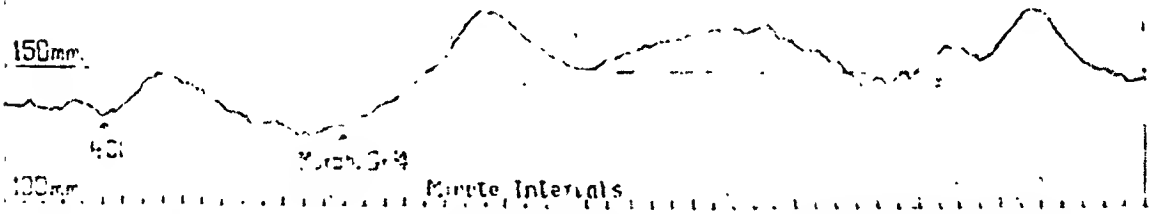


FIG. 1. Kymographic record of the resistance of the sphincter of Oddi 10 days after endocholedochal sphincterotomy.

The patient was admitted to the Mt. Sinai Hospital on March 25, 1937. She was operated upon on March 26 by Dr. Ralph Colp. The liver and gall-bladder bed appeared normal. The common duct did not appear dilated and was found to contain golden yellow bile. There was no obstruction upwards toward either hepatic duct and a probe could readily be passed into the duodenum. The pancreas showed no adenomata. No common duct stones could be felt, but on the posterior wall of the pancreas there could be felt a narrow, hard ridge running at right angles to the pancreatic duct. The nature of this ridge was difficult to determine (this accounted for the peculiar linear shadow density seen on the previous roentgen-ray). The sphincterotome was inserted into the common duct and down into the duodenum and the sphincter of Oddi was cut and a section of it removed.

A "T" tube was inserted into the common duct. The patient made an uneventful recovery. Figure 1 is a kymographic record of the resistance of the sphincter of Oddi ten days after endocholedochal sphincterotomy. The resistance was found to measure 130 mm. of water. Following intraduodenal instillation of dilute HCl, the resistance rose to 145 mm. falling to the original level in ten minutes. The hypodermic injection of morphine caused the resistance to rise to 145 mm. at which level it remained for the duration of the experiment.

Figure 2 is a typical kymographic tracing in a patient in whom the sphincter had been left intact. The original resistance (160 mm. of water) rose to 255 mm. follow-

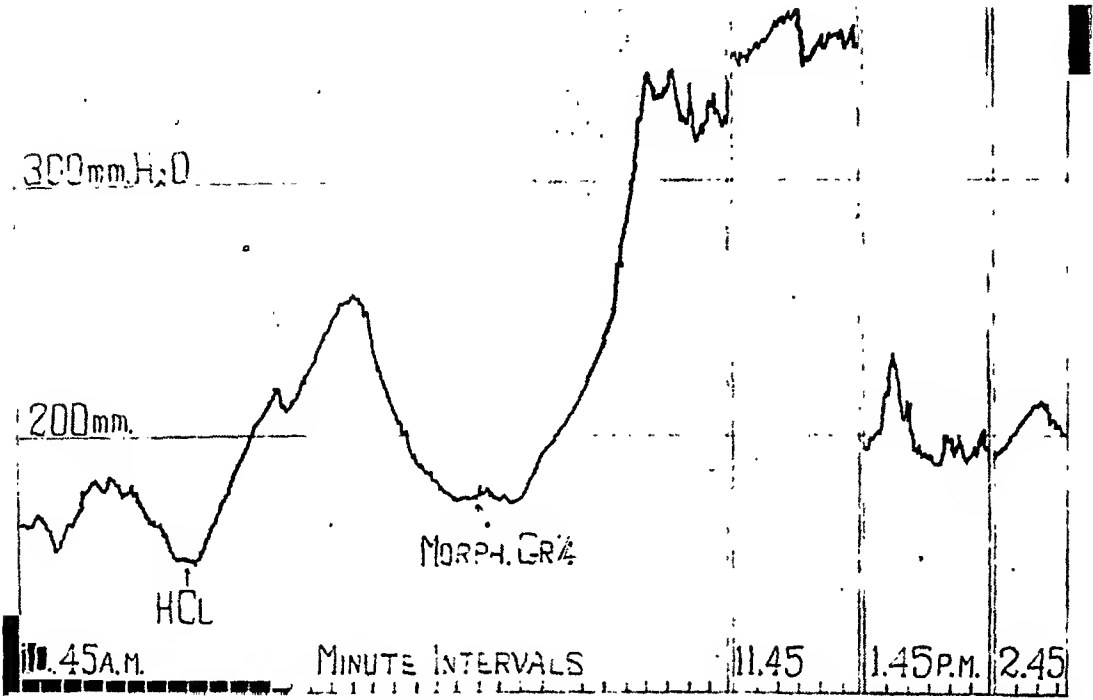


FIG. 2. Typical kymographic tracing in a patient in whom the sphincter had been left intact.

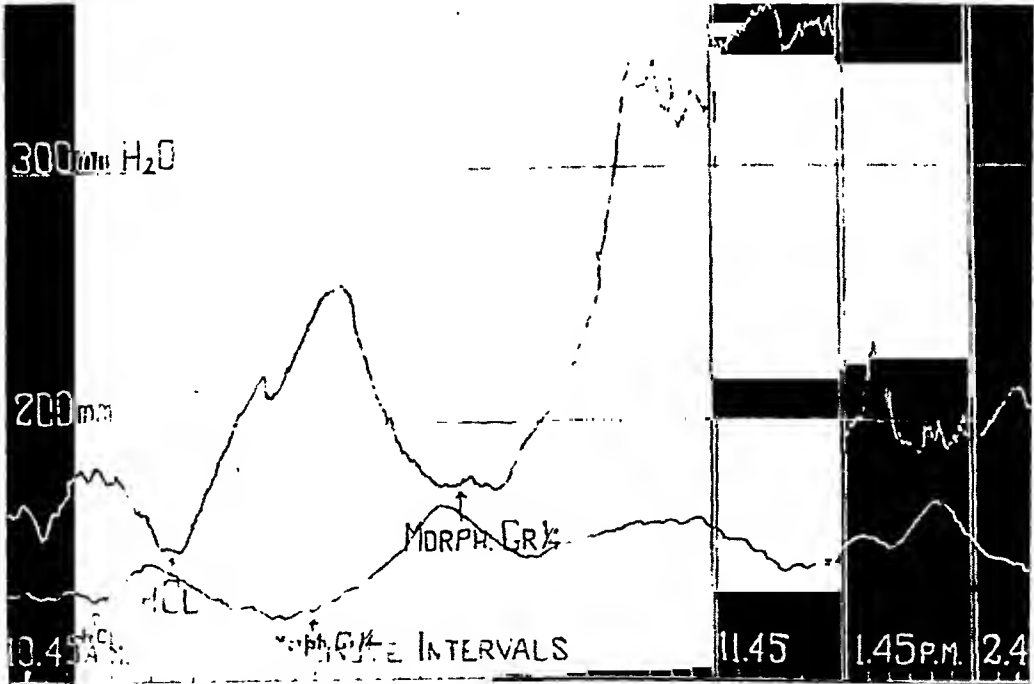


FIG. 3. The tracing from the patient in whom the sphincter of Oddi was sectioned (figure 1) superimposed upon the tracing in a patient with an intact sphincter (figure 2). The difference in the levels of the tracings clearly shows the small part played by the duodenal musculature and the important part played by the sphincter of Oddi.

ing the local application of dilute HCl. The spasm produced by morphine raised the resistance to 370 mm. of water.

Figure 3 shows the tracing from the patient in whom the sphincter of Oddi was sectioned (figure 1) superimposed upon the tracing in a patient with an intact



FIG. 4. Lipiodol study 11 days after sphincterotomy before administration of morphine.

sphincter (figure 2). The difference in the levels of the tracings clearly shows the small part played by the duodenal musculature and the important part played by the sphincter of Oddi.

Figures 4 and 5 show lipiodol study 11 days after sphincterotomy. The resistance of the common duct sphincter was so low (figure 4) that the terminal portions of the



FIG. 5. Lipiodol study in case of sectioned sphincter of Oddi after administration of morphine.

hepatic ducts and the upper end of the choledochus were not outlined before lipiodol entered the duodenum. Following the administration of morphine (figure 5) the duodenal wall was seen to become spastic, compressing the intramural portion of the

choledochus. The resultant increase in the resistance was slight, since only the terminal portion of the hepatic ducts was visualized before lipiodol entered the duodenum. These studies confirm the results of the kymographic tracing (figure 1).

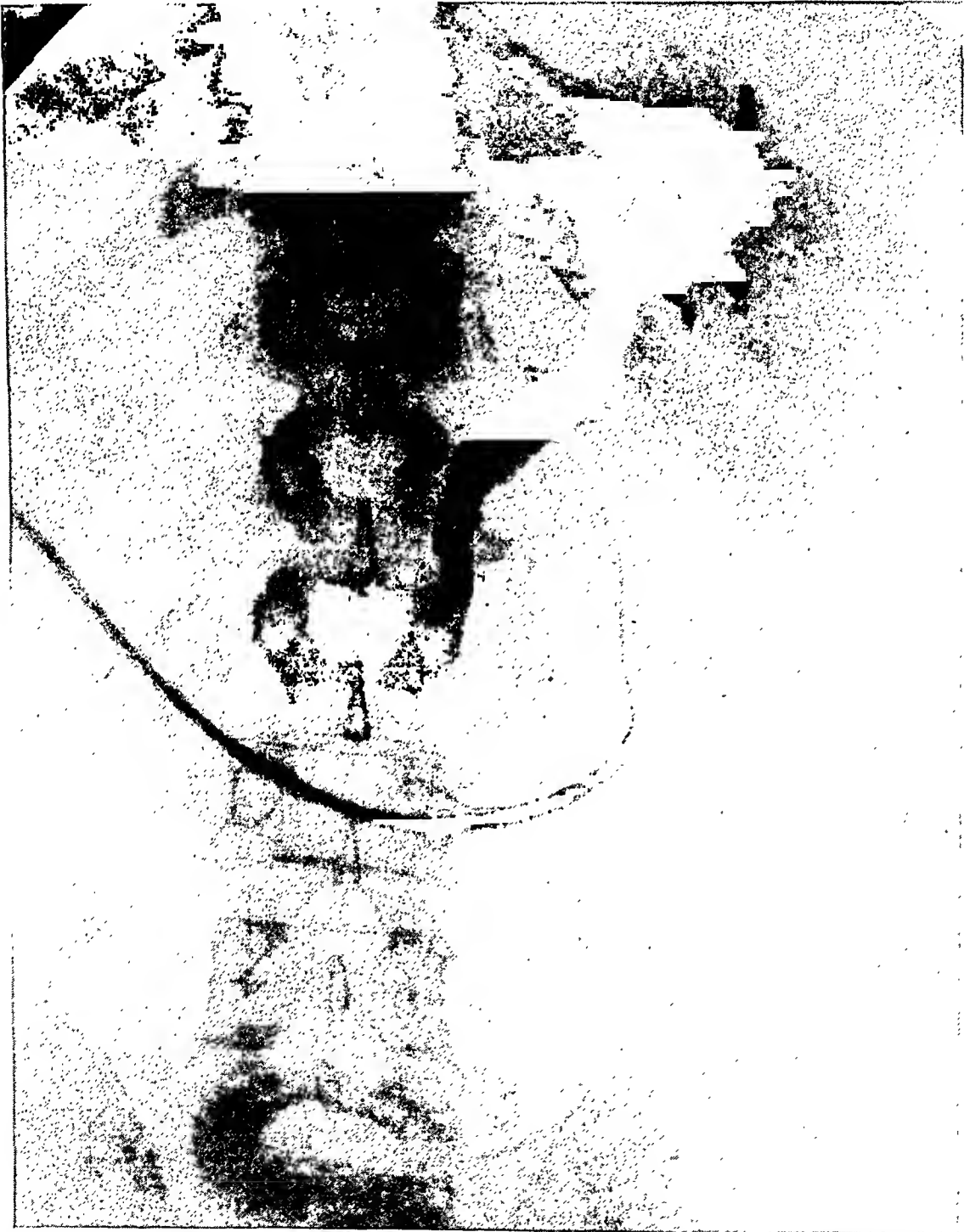


FIG. 6. Lipiodol study in patient whose sphincter was left intact before administration of morphine.

Figure 6 shows lipiodol studies before and figure 7 after the administration in the patient whose kymographic tracing is recorded in figure 2. Note that in figure 4 (manometric resistance 165 mm.) and in figure 6 (manometric resistance 160 mm.)



the terminal ends of the hepatic ducts are visualized to an equal extent. The spasm produced by morphine in the intact sphincter of Oddi (figure 7) raised the resistance to such a height (370 mm.) that the very fine biliary radicles were visualized before lipiodol entered the duodenum.



FIG. 7. Lipiodol study in patient whose sphincter was left intact after administration of morphine.

The patient was discharged from the hospital April 1937. She has been on a full diet without any medication. There have not been any attacks of biliary colic during the past year. There have been, however, episodes of hunger followed by generalized urticaria. The etiologic factor in this case, i.e. the glandular dyscrasia, still remains. The attacks of biliary colic have been avoided by sectioning the sphincter of Oddi. This procedure has made improbable the recurrence of spasm of the sphincter with its resultant increase in intraductal pressure.

### SUMMARY

The subject of spasm of the sphincter of Oddi has been briefly reviewed.

A case presenting a train of symptoms typical of this condition is reported.

A glandular dyscrasia appears to have been the etiologic factor in this case.

Cessation of the attacks of biliary colic has been obtained by surgical section of the sphincter of Oddi.

Roentgen and kymographic evidence is presented to show that an appreciable rise in intraductal pressure cannot be obtained in the presence of a sectioned sphincter of Oddi.

I wish to express my sincere appreciation to Dr. R. Colp and Dr. H. Doubilet for their kindness in presenting me with the excellent photographs which illustrate this paper.

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## SYSTEMIC POISONING DUE TO SYNTHETIC ORGANIC HAIR DYE: FATAL CASE WITH AUTOPSY\*

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HAIR dyeing, a practice of great antiquity, is still widely prevalent today. A variety of materials are used for the purpose of producing variously tinted hair. These substances fall into three groups: (1) Those of vegetable origin (henna, chamomile); (2) metallic substances (silver, manganese, bismuth); (3) synthetic compounds (paraphenylenediamine, paratoluylenediamine, pyrogallol). Because of the ease of application, the relative permanence, and supposed "naturalness" of the resulting tints, the last group has been greatly exploited in recent years. Soon after their introduction, however, as important fixtures in the cosmetic armamentarium, reports of toxic effects began to appear in medical literature.

Because of these adverse comments and of restrictive legislation adopted in some European countries and in certain states in this country,<sup>1</sup> it has been necessary for the manufacturers to change the composition of their products on several occasions. Paraphenylenediamine was the first of the synthetic compounds to be used and is still, probably, widely used even today. In the hair dye under consideration, this substance was replaced by paratoluylenediamine, a supposedly non-toxic agent. That the changed product was entirely innocuous was, however, belied by further reports of toxic manifestations. As a result, if the product was to continue to be marketed commercially, another change was necessary.<sup>2</sup> The most recent chemical substitute to be used is reported to be pyrogallol.

Medical literature abounds in descriptions of local dermatologic mishaps following the use of synthetic hair dye, usually paraphenylenediamine, but a careful review of the literature reveals reports of but few cases of systemic poisoning, and only one of these reports contains necropsy data.<sup>12</sup> It is our purpose to record a second fatal case with necropsy findings.

Since we are concerned with a hair dye which at one time or another has contained paraphenylenediamine, paratoluylenediamine and pyrogallol, it may not be amiss to briefly consider some properties of these agents. Paraphenylenediamine,  $C_6H_4(NH_2)_2$ , was first prepared by Hoffman in 1854.<sup>3</sup> In actual practice this substance when combined with hydrogen peroxide forms a product known as quinone di-imine (Bandrowski's base) which is believed to be the actual tinting agent. Hanzlik<sup>4</sup> has studied the pharmacologic effects of the phenylenediamines on rabbits. These are characterized by stimulation of the circulation and respiration, fall in body temperature, tremors, increased reflex excitability, convulsions, coma and death. The hypodermic or gastric administration of paraphenylenediamine has been noted furthermore to produce edema of the face, nose, conjunctivae and neck. This substance, under the trade name of ursol, is used to dye furs and has been known to produce dermatitides about the neck of wearers.<sup>5</sup> As a purely industrial hazard, it has long been known

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to lead to asthmatic-like attacks in fur workers<sup>6</sup> and is, moreover, a toxic hazard in the rubber industry where it is used as an accelerator of the process of vulcanization.<sup>7</sup> The toxic effects, noted in profusion in medical literature in the early years of this century were chiefly of a local dermatological nature.<sup>8</sup> The further use of this compound to dye the eyelashes was followed by various ophthalmic complications ranging from conjunctivitis to corneal necrosis and even death.<sup>9</sup> Cases of systemic poisoning have been reported by Nott,<sup>10</sup> Close,<sup>11</sup> and Israels and Susman.<sup>12</sup> The former, in 1924, cited a case which was characterized by an acute onset, marked cyanosis and prostration. These symptoms bore a marked resemblance to those produced by acute aniline poisoning. In 1932 Close reported a case with symptomatology of a neurological and gastrointestinal nature. The manifestations included nystagmus, tinnitus, giddiness, headache, flatulence and anorexia. Recovery followed shaving of the head of the patient.

Of considerably more interest is the first recorded fatal case reported by Israels and Susman in 1934. Their patient, a young woman, who worked as a dyer in a hairdressing establishment, complained of jaundice, weakness, headache, sore-throat and joint pains. Slight hepatomegaly was present on examination. The Van den Bergh reaction was of the prompt direct positive type. Other laboratory data revealed a moderate anemia, slight leukopenia and diminution in platelets. No accurate data concerning red cell size were given. The patient's course, under observation, was rapidly downhill and was marked by steadily increasing jaundice. Postmortem examination revealed a coarsely nodular liver somewhat diminished in size, ascites, moderate splenomegaly and scattered purpuric hemorrhages on the skin and gastric mucosa. On microscopic examination of the liver the authors found what they termed "typical features of subacute yellow atrophy."

As a corollary to the liver damage which appears as the outstanding pathological finding in the above case and in the one to be presented, it is of interest to note the three cases reported by Baldrige<sup>13</sup> in 1935. He found in these patients macrocytic anemias with aplastic features, associated with the periodic application of synthetic organic hair dyes. In two cases the active dyeing agent was reported as paraphenylenediamine and in the other toluylenediamine. Two had definite macrocytosis by volume index and all showed varying degrees of anemia, leukopenia and thrombocytopenia. Liver function tests were not reported, nor was any mention made of jaundice. Improvement apparently followed cessation of dyeing. No explanation beyond possible idiosyncrasy is offered by Baldrige for these occurrences. The rôle of liver damage in the causation, at times of macrocytic anemia has been stressed in the last few years.<sup>14</sup> It is commonly stated that there is a failure by the liver in such cases to properly store or utilize the anti-anemic factor of Castle. This simple explanation, it is true, is objected to by some authorities including Minot,<sup>15</sup> but the fact remains that, whatever the mechanism, it is the experience of all that liver damage carries with it a definite incidence of macrocytic anemia. The macrocytosis, moreover, may be a transient one depending on such transient hepatic damage as occurs in so-called catarrhal jaundice and chronic passive congestion.<sup>16</sup> It would seem to us, then, in the light of the above facts and the demonstrated liver lesions in Israels and Susman's case and in the present one that there is at hand a ready

explanation of the macrocytosis observed by Baldrige. This evidence of dyshemopoiesis was a prominent feature of the case to be presented.

Toluylenediamine,  $C_6H_3(NH_2)_2$ , a closely allied chemical product, was used over a period of years as a substitute for paraphenylenediamine. The pharmacological activities of this agent have been known for many years. It will produce marked jaundice in experimental animals. The mode of production has been disputed, some observers asserting it to be of a hemolytic nature, while others claim it to be the result of toxic liver damage. Wolff<sup>17</sup> has recently demonstrated that apparently the latter view is correct, i.e. there is actual hepatic parenchymal damage in the nature of a toxic hepatitis.

Pyrogallol,  $C_6H_3(OH)_3$ , the most recent dyeing constituent, is potentially a toxic hazard. Sollman<sup>18</sup> states that it may produce an intense acute nephritis, form methemoglobin and cause hemolysis of red blood cells. We are not aware of reports of deleterious effects, specifically attributable to this product when used as a hair dye.

With this brief survey of the grimmer aspects of hair dyeing we wish to record a case of toxic cirrhosis of the liver, terminating fatally and subsequently necropsied, in which there was a history of repeated, long-continued application of synthetic organic hair dye.

#### CASE REPORT

M. O'S. a white female, aged 61, a practical nurse by occupation, was admitted to the medical service of Dr. M. C. Pincoffs at Mercy Hospital on September 6, 1935. The presenting complaints were "weakness and abdominal swelling of several weeks' duration." Her illness dated back nine months to January 1935, when, as was later ascertained, she had had her hair dyed with a synthetic organic dye and just subsequent to its application had received a permanent wave. This was the last time the hair dyeing procedure was carried out, but it was ascertained that she had been accustomed to have her hair dyed on an average of every two months over a period of 15 years and had continuously used the same product. The coincidence of the permanent wave with the dyeing procedure was believed to have occurred only this time. Soon after, during January, she experienced attacks of epistaxis which seemed to occur in association with excitement. The occurrence of a domestic tragedy at this time produced a "nervous breakdown" to which was attributed many symptoms which ensued. These included ready fatigability and episodes of dull aching pain over the precordium and in the left lower quadrant of the abdomen. Early in July 1935, she first became aware of a mass in the left upper abdomen, and mild edema of the ankles appeared at this time. On the advice of a physician the patient spent five weeks in bed with resultant disappearance of the edema. Late in August an attack of diarrhea associated with melena occurred and lasted about two days. Hospitalization was advised soon after.

Further questioning revealed a history of anorexia, constipation of 3 to 4 years' duration, abdominal distention of several weeks' duration and loss of 20 pounds in weight during the nine months of illness. Exertional dyspnea had been noted during the year preceding admission and edema of the ankles for two months. Nocturia, two to three times, was present.

The family history was entirely non-contributory. An attack of typhoid fever had occurred about 1905. A history of several so-called gall-bladder attacks associated with jaundice was elicited, but the exact dates could not be ascertained. Menopause had occurred six years before, but an episode of vaginal bleeding of three days' duration was present one year later.

Examination, on admission, revealed an elderly, somewhat obese, white female, who was lying quietly in bed. Graying of the roots of the hair merging into a brownish color at the free ends was noted. There was complete adentia. The papillae of the tongue were present. Examination of the heart and lungs was essentially negative. The blood pressure was 106 systolic and 60 diastolic. The abdomen was obese and symmetrically distended. Tenderness was elicited on pressure in the right upper quadrant of the abdomen. In the left upper quadrant a mass, identified as spleen, was noted extending to the midline and from the costal margin to the level of the umbilicus. Several ecchymotic patches were noted on the right leg and one on the left. The reflexes were normal and no pathological reflexes could be obtained.

Pelvic examination revealed no abnormality. Inspection of the fundi revealed a few scattered, whitish, retinal spots, which were believed by the ophthalmologist to be congenital in origin.

A number of roentgen-ray studies were made including a gastrointestinal series, pyelograms and films of the long bones and chest. The abdominal roentgenograms revealed the presence of an extra visceral mass (spleen) in the left upper quadrant causing a pressure deformity of the stomach and interfering with the emptying of the left renal pelvis. The other films were completely negative.

The comprehensive laboratory studies can be summarized as follows: Repeated urinalyses were negative except for the appearance of urobilin terminally. Blood chemical determinations showed normal values for sugar and urea throughout. The Van den Bergh reaction was prompt, direct, positive. The blood bilirubin rose from 0.625 mg. to 30 mg. terminally. The bromsulphalein test of liver function revealed 20 per cent retention of dye at the end of two hours. Blood Kolmer and Kahn tests were negative. Aside from the presence of occult blood on several occasions, stool examinations were also essentially negative. Gastric analysis revealed normal values for both free and total acid.

The hemocytological picture on admission was as follows: Hemoglobin, 74 per cent (12.2 gm. Sahli); red blood cells, 3,840,000; white blood cells 2,250. The differential count showed: Polymorphonuclear neutrophils, 76 per cent (6 per cent staff forms); lymphocytes 19 per cent; monocytes 6 per cent. Further blood pictures during the course in hospital revealed a steady diminution in hemoglobin, red and white blood cells. The latter, however, increased terminally to 10,250 under the influence of a localized septic infection.

The bleeding time was three minutes and the coagulation time five minutes. A fragility test revealed incipient hemolysis in saline solution at 0.35 per cent and complete hemolysis at 0.25 per cent. Platelet counts varied from 38,500 to 65,400 (Olef technic; normal, 500,000) and the Rumpel-Leede phenomenon was positive. A Price-Jones graph revealed definite widening of the base and a distinct shift to the right. The mean corpuscular volume was 114 cu. microns and the volume index 1.2. Reticulocyte counts varied from 2.2 per cent to 7 per cent, the latter being obtained seven days after the institution of adequate intramuscular liver therapy. Sternal bone marrow, obtained by the puncture method, revealed slight normoblastic increase as well as increase in percentage of lymphocytes, but no other deviations from normal.

The patient's stay in the hospital totalled 55 days and during the first four weeks of this period her temperature, pulse and respirations remained within normal limits. She became somewhat irrational about three weeks after admission, apparently coincidentally with an increase in jaundice. Three attacks of epistaxis of moderate severity occurred about one month after admission. Neurological re-examination, several weeks after entrance to the hospital, revealed impairment of proprioceptive sensation and apparent loss of vibratory sensation below the third lumbar vertebra. On October 20, five weeks after admission, an abscess of the left buttock, at the site of an intramuscular injection of liver, was noted. This required incision and drainage and was associated with a septic temperature which continued

until death. Liver therapy, as has been stated, produced some reticulocytosis, but no specific increase in red cell count. The patient was treated symptomatically with daily intravenous glucose injections, but steadily became more toxic and irrational. Pitting edema of the lower extremities and distention of abdomen were pronounced terminally. The patient gradually lapsed into coma and died November 1, 1935, approximately eleven months after the onset of symptoms.

### AUTOPSY

Necropsy was performed eight hours after death. The following report is abbreviated, but no pertinent data are omitted. The external examination revealed an elderly, obese, white female, who was markedly jaundiced. The hair of the scalp displayed a variegated appearance with that portion closest to the roots being gray and the free ends of a reddish-brown color. The abdomen was quite distended.

The peritoneal cavity contained 2,000 c.c. of clear, yellow, serous fluid. The spleen was enlarged and extended five cm. below the left costal margin. The liver appeared small and was tucked up beneath the right costal margin. The pleural cavities displayed no changes of significance aside from the presence of a few fibrous pleural adhesions at the left apex.

The heart was of normal size and displayed no unusual gross changes beyond yellowish discoloration of the mural and valvular endocardium whose appearance was shared by other serous surfaces. Slight atherosclerotic changes were evident in the aorta. Hypostatic changes were seen in both lungs macroscopically.

The liver weighed 1150 gm. Its external surface was of a coarse, diffusely nodular appearance. These nodules varied in size from three mm. to one cm. and were brownish-green in color. The intervening depressions were gray-brown. The capsule appeared somewhat thickened, but translucent (figure 1). Increased resistance was met with on sectioning. The cut surface revealed complete distortion of the normal architecture, due to diffuse nodulation. These deep nodules were of similar appearance to those of the capsular surface. The gall-bladder and biliary passages were devoid of gross lesions.

The spleen weighed 700 gm. It was of normal consistency and presented a smooth, glistening, taut capsule. The cut surface was of a dark, wine-red color and the Malpighian bodies were obscure.

The entire genito-urinary apparatus was free of any noteworthy change. Examination of the gastrointestinal tract likewise revealed no gross pathologic lesion. The adrenals, macroscopically, were normal.

Permission to examine the brain and spinal cord was not obtained.

The important histopathological changes were noted in the liver and spleen. In addition, a terminal lobular hypostatic pneumonia was present in the lower lobes of both lungs. The presence of bile pigment was noted in the tubular epithelium of the kidney and in the adrenal cortex.

Sections of the liver showed marked distortion of the normal architecture, due to the presence of broad, anastomosing bands of dense, but cellular connective tissue which completely destroyed the preëxisting lobular arrangements (figure 2). The remaining groups of parenchymal cells displayed various degenerative and necrobiotic changes (figure 3). Numerous large, fat vacuoles were seen in many cells. Others were edematous and showed granular cytoplasmic changes with resultant marked sinusoidal narrowing. Still others had progressed to complete necrosis, with pyknotic, karyorrhectic and karyolytic nuclear changes. Many cells displayed marked bile pigmentation. The intervening fibrous tissue was the seat of a diffuse lymphocytic invasion and displayed the presence of numerous abortive bile canaliculi and thin-walled blood spaces. The extensive fibrosis suggested obliteration of whole lobules of liver parenchyma.

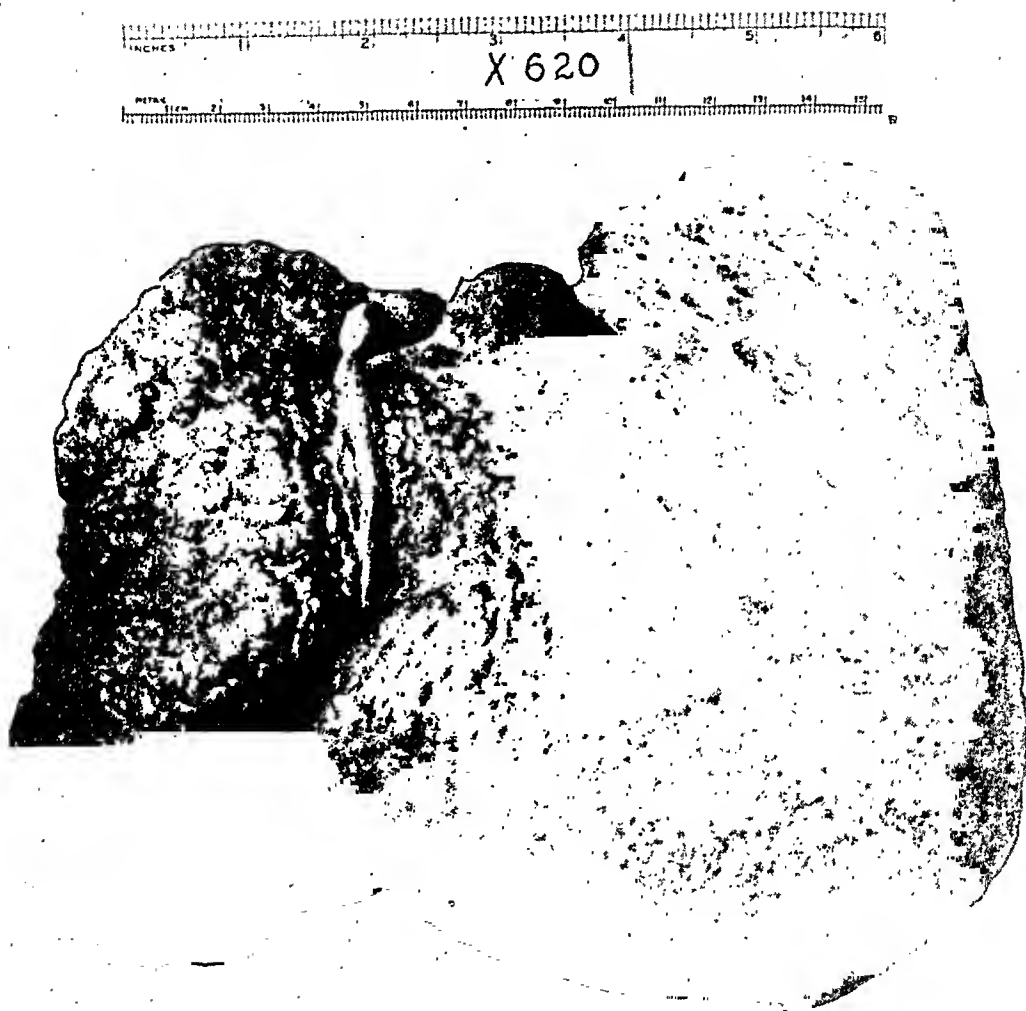


FIG. 1. Liver is diminished in size and presents a coarsely nodular surface.

Sections of the spleen revealed a normally cellular and distinctly congested pulp with the reticulum and sinuses sharing the latter. Occasional clumps of brownish-green pigment were observed within reticular cells. The Malpighian bodies were of normal histological structure.

The anatomical diagnosis may be stated as follows: Subacute yellow atrophy of the liver; chronic passive congestion of the spleen (splenomegaly) and gastrointestinal tract; ascites (2,000 c.c.); jaundice, severe; lobular pneumonia, bases, bilateral.

#### COMMENT

The etiological concepts of toxic cirrhosis or healed yellow atrophy have been considerably broadened since the relationship between this fibrotic stage and an earlier necrotic process was established by Mallory.<sup>19</sup> Many inorganic and organic chemicals entering the body by a variety of routes such as ingestion, inhalation and injection are known to produce severe hepatic parenchymal damage. The more commonly known of these include phosphorus, arsphenamine, chloroform, cinchophen, carbon tetrachloride and phenylhydrazine. In this in-



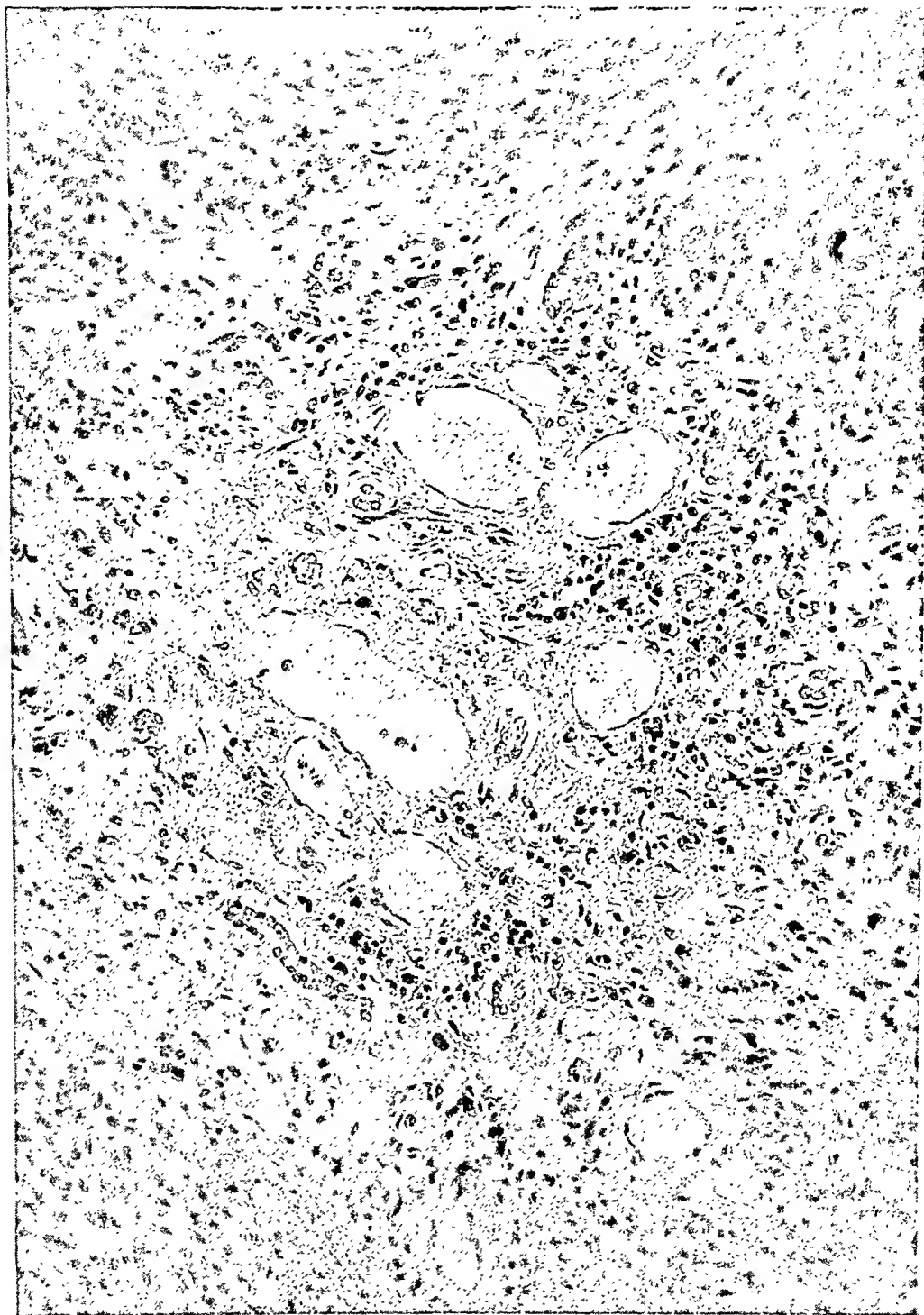


FIG. 2. Liver. Distortion of architecture by broad anastomosing bands of fibrous tissue. Note lymphocytic infiltration, presence of numerous dilated vascular spaces and proliferating bile canaliculi.  $\times 100$ .

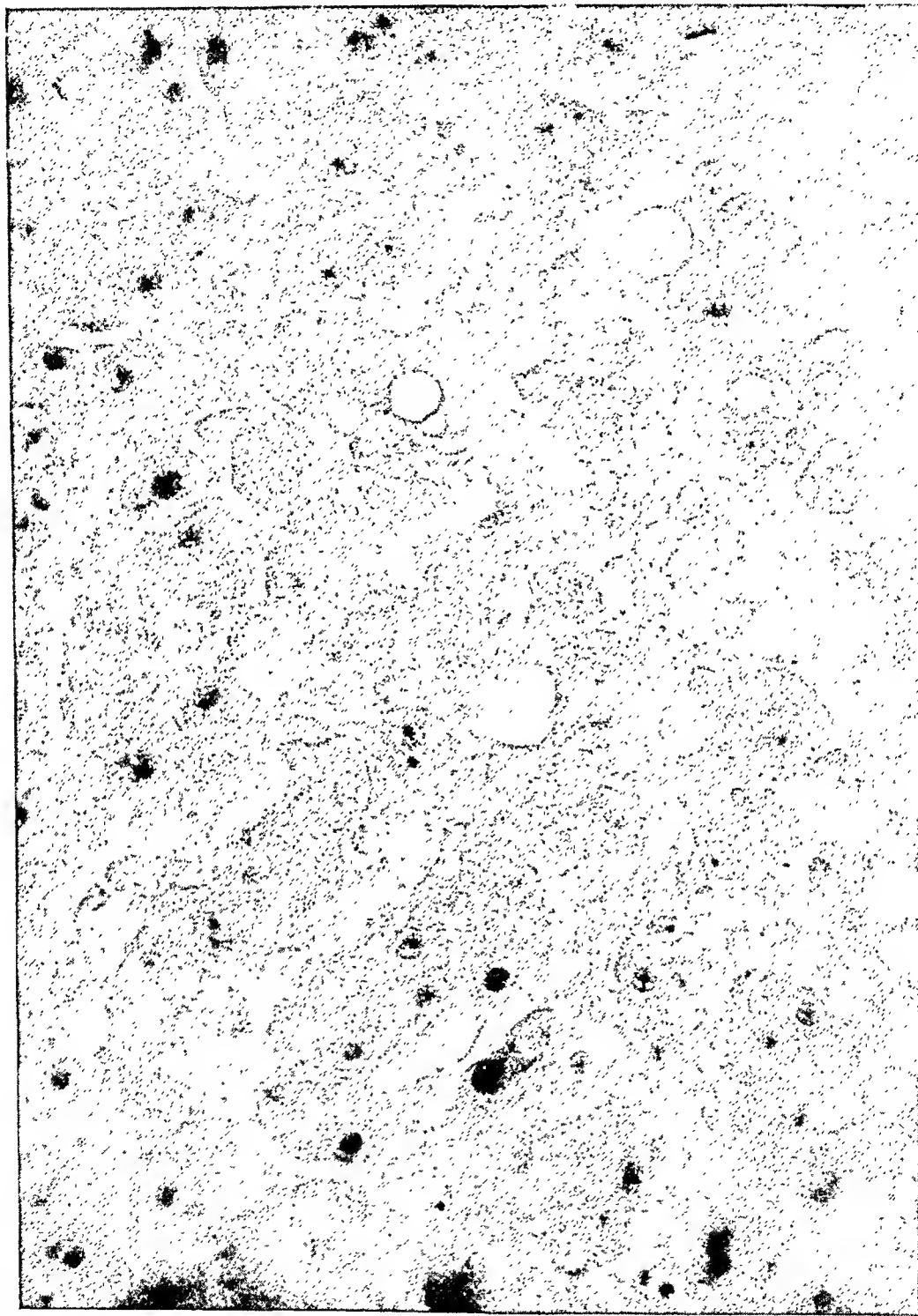


FIG. 3. Liver. Note fat vacuolization and necrobiotic changes in remaining parenchyma.

dustrial era the possibility of contact with many, as yet unknown, hepatotoxins increases immensely. Paratoluylenediamine has long been known to produce severe jaundice, the pathogenesis of which has been recently shown to be due to liver parenchymal damage. The use of this substance had apparently been largely confined to experimental procedures until it was found to be commercially useful as a hair dye. The first necropsied fatal case of hair dye poisoning in 1934 revealed marked liver damage. This was attributed to paraphenylenediamine by the authors who stated that theirs was the first recorded instance of hepatic injury. Their report does not include any data concerning the actual commercial preparation used. Because of the widespread use of paraphenylenediamine, both as a cosmetic and in industry, this rarity of liver damage is difficult to explain. Moreover, pharmacological studies of the toxic effects of the phenylenediamines reveal no evidence of liver damage. It appears quite probable, to us, that a commercial hair dye of secret and changing composition could have contained paratoluylenediamine, a known hepato-toxin, at the time this fatality was recorded. The report of Baldridge likewise fails to reveal any careful correlation between the dyeing constituents and the macrocytosis which he observed.

A careful consideration of the literature of hair dye poisoning reveals the fact that dermatological complications occurred in profusion during a time when paraphenylenediamine was widely used. The two autopsied fatal cases (including the present report) occurred during a time when exposure to paratoluylenediamine was possible.

To recapitulate briefly then, we may state that the demonstration of paratoluylenediamine as an experimental hepatotoxic substance, the occurrence of two necropsy proved cases of severe liver damage in patients exposed to its effects in a hair dye, the absence of any other known etiological factor in these patients, and the citation of three cases of atypical macrocytic anemia in persons using the dye appear to offer some tenable evidence for regarding the association of the two factors of hair dyeing and liver pathology as more than mere coincidence.

The incidence of liver damage in persons who have been exposed to this chemical agent is extremely difficult to ascertain. It would seem that it is somewhat infrequent. The toxic action may be on the basis of personal idiosyncrasy such as is exhibited to so many other coal-tar derivatives. It has been suggested by Baldridge that the heat and ammonia used during the application of a "permanent wave" may have aided in the rapid absorption of the dye and the onset of symptoms in his cases. It is notable that the coincidence of these two procedures occurred in our case just prior to the onset of symptoms. The limited data offered by the two necropsied cases do not permit of wide generalizations, but offer an interesting avenue of inquiry in cases of jaundice of obscure etiology in females.

#### SUMMARY

1. Toxic effects from synthetic hair dyes have been frequently reported in medical literature. Most have been of a local dermatological nature. Several cases of systemic poisoning have been noted in the literature, only one of which resulted fatally and was necropsied.

2. The synthetic group of dyes includes those frequently used today. Among

these are paraphenylenediamine, paratoluylenediamine and pyrogallol. Paratoluylenediamine is a known hepatotoxin.

3. A case is reported of prolonged use of a synthetic hair dye followed by a fatal illness which was characterized clinically by severe jaundice, splenomegaly, macrocytic anemia and beginning postero-lateral cord changes. Pathological, toxic cirrhosis of the liver was the outstanding feature. This is apparently the second necropsied case in medical literature.

4. Evidence supporting the relationship between the use of synthetic organic hair dyes and liver damage is offered.

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## EDITORIAL

### *FURTHER ADVANCES IN THE TREATMENT OF PELLAGRA AND ASSOCIATED DEFICIENCY DISEASES*

In an editorial in the March 1938 number of the *ANNALS* we pointed out the relatively unsatisfactory results obtained by the usual methods of treating pellagra and discussed the striking improvement noted in the earliest reports regarding the administration of nicotinic acid to patients with this disease. During the year and more that has since elapsed, a large number of patients with pellagra have been treated with nicotinic acid by many different observers, and in general the successful results reported in the early experiments have been amply confirmed. Even if the patients are kept on the deficient pellagra-producing diet, the administration of nicotinic acid brings about an abrupt, dramatic improvement. This is shown particularly in the prompt subsidence of the stomatitis and of the inflammatory changes in the other mucous membranes, in relief from the general malaise, anorexia and digestive disturbances and in the disappearance of the mental confusion and the psychoses, at least in the early acute stages. The cutaneous lesions proved relatively resistant, although the erythema also disappears.

These observations, however, have also confirmed the clinical impression previously held by many that pellagra as it occurs naturally is a multiple deficiency disease and cannot be attributed entirely to a lack of any one single substance. If patients with pellagra are kept on the deficient diet but given adequate quantities of nicotinic acid, in many cases there is a persistence or a recurrence of certain disease symptoms. The most frequent and prominent are numbness, paresthesias, pains and even paralyses which are manifestations of a peripheral neuritis. These are especially marked in alcoholic addicts, but are common among endemic cases also. It has been shown, especially by Spies and his associates,<sup>1</sup> and by others also, that they are manifestations of an associated beriberi and can be cured by the administration of crystalline vitamin B<sub>1</sub>.

The administration of both thiamin and nicotinic acid does not restore to normal health an individual kept on such a restricted diet. Various symptoms may persist or eventually appear which, in large part at least, are attributable to riboflavin deficiency. This vitamin was the first to be isolated and identified from the old vitamin B<sub>2</sub> complex. Its structural formula is known and it has been synthesized. In the body after phosphorylation it is combined with a protein nucleus to form an oxidizing enzyme which is believed to be present in, and essential for the vital activities of all living cells.<sup>2</sup> In rats a deficiency of this substance causes retardation of growth, chronic

<sup>1</sup> SPIES, T. D., and ARING, C. D.: The effect of vitamin B<sub>1</sub> on the peripheral neuritis of pellagra, *Jr. Am. Med. Assoc.*, 1938, cx, 1081-1084.

<sup>2</sup> BOOHER, L. E.: Chemical aspects of riboflavin, *Jr. Am. Med. Assoc.*, 1938, cx, 1105-1111.

ill health, the appearance of areas of alopecia and dermatitis about the ears, neck, chest and lower legs, and the development of cataract.<sup>3</sup> It was obvious that a substance of such fundamental importance must be essential in human nutrition, but symptoms distinctive of a deficiency in man hitherto have eluded observation.

Recently Sebrell and Butler<sup>4</sup> have described a typical symptom complex which appeared in a group of individuals who were kept on the pellagra-producing diet of Goldberger and Tanner<sup>5</sup> supplemented by ascorbic acid and thiamin chloride and (after symptoms of pellagra appeared) nicotinic acid. In most of these individuals after three to four months, in addition to general malaise, weakness and loss of weight, lesions resembling perlèche appeared about the angles of the mouth. The mucosa at these points looked pale, then became moist and macerated but not inflamed, and was covered with a honey-colored crust which could be removed without causing bleeding. Transverse fissures appeared exactly in the angles, occasionally extending laterally for a centimeter onto the skin. Medially they extended slightly downward but did not involve the buccal mucous membrane. The lips looked intensely red along the line of closure. These observers also noted redness and a seborrheic desquamation of the skin about the nasolabial folds, the alae of the nose and about the ears and eyes. These symptoms were not influenced by nicotinic acid, but were relieved within a few days by synthetic riboflavin.

Similar lesions, often designated "angular stomatitis," have been described by a number of writers, notably by Stannus,<sup>6</sup> in outbreaks of deficiency diseases in the tropics. These have been regarded usually as a manifestation of pellagra, or of a deficiency of vitamin B<sub>2</sub> in the old sense, but not specifically as due to lack of riboflavin. Vilter, Vilter and Spies,<sup>7</sup> however, independently recognized the occurrence of riboflavin deficiency as a complication in their pellagra cases, and Spies, Bean and Ashe<sup>8</sup> have recently discussed this feature in greater detail. They confirm Sebrell and Butler's description of the lesions, and note that the condition may occur independently of or in association with beriberi or pellagra.

These authors<sup>9</sup> have also found that some of the patients with pellagra who were treated merely by the administration of these synthetic vitamins

<sup>3</sup> HOGAN, A. G.: Riboflavin: Physiology and pathology, Jr. Am. Med. Assoc., 1938, cx, 1188-1193.

<sup>4</sup> SEBRELL, W. H., and BUTLER, R. E.: Riboflavin deficiency in man (a preliminary report), Pub. Health Rep., 1938, liii, 2282-2284.

<sup>5</sup> GOLDBERGER, J., and TANNER, W. F.: A study of the pellagra-preventive action of dried beans, casein, dried milk and brewers' yeast, with a consideration of the essential preventive factors involved, Pub. Health Rep., 1925, xl, 54.

<sup>6</sup> STANNUS, H. S.: Pellagra and pellagra-like conditions in warm climates, Trop. Dis. Bull., 1936, xxxiii, 729, 815, and 885.

<sup>7</sup> VILTER, R. W., VILTER, S. P., and SPIES, T. D.: Relationship between nicotinic acid and a codehydrogenase (cozymase) in blood of pellagrins and normal persons, Jr. Am. Med. Assoc., 1939, cxii, 420-422.

<sup>8</sup> SPIES, T. D., BEAN, W. B., and ASHE, W. F.: Recent advances in the treatment of pellagra and associated deficiencies, Ann. Int. Med., 1939, xii, 1830-1844.

<sup>9</sup> SPIES, T. D., BEAN, W. B., and ASHE, W. F.: A note on the use of Vitamin B<sub>2</sub> in human nutrition, Jr. Am. Med. Assoc., 1939, cxii, 2414.

continued to complain of nervousness, irritability, abdominal pain and marked weakness, although the specific manifestations of pellagra and beriberi were relieved. In four such cases they report that the intravenous injection of 50 milligrams of synthetic Vitamin B<sub>6</sub> afforded dramatic relief of these symptoms within twenty-four hours.

What other deficiencies may also lurk in the pellagra-producing diet can be determined only by future studies. There is already ample proof that the deficiency is complex. Although nicotinic acid is invaluable in the treatment of severe cases of pellagra, the simple administration of this substance will not suffice to restore normal health and nutrition. It is most important that those who treat patients with pellagra realize the frequency of these associated deficiencies and watch for them. Many patients need thiamin, and many, probably, will need riboflavin as well.

These vitamin preparations, however, must be regarded primarily as temporary aids to be used in emergencies for the relief of acute deficiency symptoms. The ultimate aim should be the institution of an adequate, well balanced diet. Only in this way can there be any assurance of maintaining normal nutrition. The measures by means of which pellagra might be controlled are now fairly well understood. This disease, however, promises to remain a serious problem in the South unless economic conditions can be so far improved that the poorer classes can and will provide themselves with an adequate diet.

P. C.



## REVIEWS

*Principles of Hematology.* By RUSSELL L. HADEN, M.A., M.D., Chief of the Medical Division of the Cleveland Clinic, Cleveland, Ohio; formerly Professor of Experimental Medicine in the University of Kansas School of Medicine, Kansas City, Kansas. 348 pages; 14.5×23.5 cm. Lea and Febiger, Philadelphia. 1939. Price, \$4.50.

In its scope this book follows quite closely the usual text on hematology, but it differs notably in the manner in which the subject is handled.

In planning this book the author states that he aimed primarily "to simplify the study of the disorders of the blood for the student and physician." This he has accomplished very successfully. He has made unusually free use of graphic methods to illustrate important points in the morphology and physiology of the blood cells. Ingenious diagrams and charts, many of which are taken from various journal articles of the author, make up a large proportion of the 155 text figures.

He has stressed the point that alterations in the number and morphology of the circulating blood cells are indications of disturbed physiology of the blood forming organs. These disturbances are discussed in detail, from the standpoint of etiology, recognition, and treatment.

The technic of the simpler laboratory procedures is given in detail, and their significance is discussed. The more complicated procedures which require expert knowledge, such as supravital staining and marrow puncture, are omitted.

There are numerous photomicrographs illustrating the various types of blood cells, and films from most of the more important diseases of the blood. The symptomatology of these conditions is covered largely by means of synopses and comments on 100 selected case histories, embracing the entire field of clinical hematology.

The book is more than a mere reiteration of the elementary facts and principles of hematology. Its most distinctive feature is the original and stimulating manner in which the material is presented. It is not recommended as a compendium, but it will be of great value both to teachers and students of the subject.

P. W. C.

*Histological Technique for Intracranial Tumours.* By DOROTHY S. RUSSELL. vi+71 pages, with 6 plates; 22.5×14 cm. Oxford University Press, London. 1939. Price \$2.50.

This book will be found an excellent guide for the technic of handling and staining tissue from the nervous system. The methods presented are those which the author has selected for use in her own laboratory, and confusion is eliminated by the omission of many optional methods. In larger treatises on the subject, the uninitiated often finds difficulty in selecting the method of choice from the many modifications of technic which are usually described. The methods given are those which are generally in use in most neuropathological laboratories, and have been found satisfactory both for the study of intracranial tumors and for general study of the nervous system. The book contains concise notes for the handling, fixation, and embedding of tissues. There is a full presentation of the accepted methods for staining embedded sections. Methods for handling frozen sections are given with adequate detail. The section dealing with metallic methods is brief but to the point. The author should have included Cajal's reduced silver method for staining neurofibrils in addition to that of Bielschowsky. The chapter dealing with the rapid diagnosis of biopsy material is of interest, and an outline is given for the proper choice of staining methods for

various types of tumors. The book contains a small number of photomicrographs, which are well reproduced. A larger number of such illustrations, however, would have added to the value of the book. The book can be recommended, and will be of service in any neuropathological laboratory.

J. G. A., JR.

*Practice of Medicine.* By JONATHAN CAMPBELL MEAKINS, M.D., LL.D., Professor of Medicine and Director of the Department of Medicine, McGill University; Physician in Chief, Royal Victoria Hospital, Montreal, etc. 1365 pages, 521 illustrations, indexed; 26 × 17.5 cm. C. V. Mosby Company, St. Louis. 1938. Price, \$12.50.

The second edition of this valuable textbook of medicine continues the excellencies of the first. In a work of this type, it is always possible for a reviewer to take exception to some statements or to criticize the author's judgment in regard to omissions and inclusions. It should be mentioned that the fourth lead of electrocardiograms does not conform to recently adopted standards; however, this is noted in the legends of such figures. The author still uses the old nomenclature for bundle branch block. Sulphanilamide is rather briefly discussed as a chemotherapeutic agent. It is not to be expected that any discussion of sulphapyridine should be found in the present edition. The carotid sinus syndrome seems entitled to more attention than a brief mention in the paragraphs dealing with epilepsy. The rôle of the carotid body as a chemoreceptor active in the control of blood pressure and respiration is not mentioned in the discussion of that structure. However, no useful purpose is served by such minor criticisms, and the reviewer unreservedly recommends this work to practitioners and students.

W. S. L., JR.

*The Language of the Dream.* By EMIL A. GUTHEIL, M.D. 286 pages; 24 × 16 cm. The Macmillan Co., New York. 1939. Price, \$3.50.

This book is very readable, in the sense that it is short and its language is remarkably free from the "jargon" that so confuses physicians who wish to learn something about psychiatry and psychoanalysis. In addition, the material is copiously illustrated with brief, concise and understandable case reports, diagrams and reproductions of drawings by patients.

The author is a pupil of Wilhelm Stekel, who founded a school of psychoanalysis, differing in some respects from the so-called "orthodox Freudian school." Because of these differences, followers of Sigmund Freud may object to some of the theories and interpretations presented in this book.

The book consists of seven chapters and a rather thorough bibliography. The first four chapters cover the theoretical aspects, with a very adequate description of symbols and their common meanings. In these chapters case reports and examples are freely used. The fifth chapter describes the technic of dream analysis, again with many illustrative examples. The sixth chapter discusses many neurotic conditions and how they specifically influence dreams. The last chapter is devoted to a consideration of the differing schools of psychoanalytic thought with especial reference to their use and interpretation of dreams.

For physicians who wish to learn something about the psychoanalytic theories regarding the meaning and interpretation of dreams, particularly regarding their use in psychotherapy, this is about the best introductory book the reviewer has seen.

H. W. N.

*Insulin: Its Chemistry and Physiology.* By HANS F. JENSEN, PH.D. xii + 252 pages; 16 × 23.5 cm. The Commonwealth Fund, New York; Oxford University Press, London. 1938. Price, \$2.00.

In this small monograph Dr. Jensen has successfully "endeavored to give a comprehensive review of the latest developments in the chemical and physiological investigations of insulin." The fact that over 1300 separate references have been consulted up to 1938 attests to the thoroughness of the author's work. While emphasis is placed on the chemistry and physiological action of insulin, adequate chapters are also given on the history, preparation, standardization and administration of this drug. In addition every physician will be interested in reading the chapter on insulin substitutes. Noteworthy is the warning that blood sugar reducing substances should be subjected to thorough animal experimentation before administration to the diabetic patient. Dr. Jensen's monograph can be heartily recommended to all readers interested in this fascinating subject.

E. G. S.

# COLLEGE NEWS NOTES

## GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of publications by members are gratefully acknowledged:

### *Books*

- Dr. Alpheus F. Jennings, F.A.C.P., Detroit, Mich., "Typhoid Fever" (by the late Charles G. Jennings, M.A.C.P.);  
Dr. Wallace M. Yater, F.A.C.P., Washington, D. C., "Fundamentals of Internal Medicine."

### *Reprints*

- Dr. Hugo O. Altnow, F.A.C.P., Minneapolis, Minn.—11 reprints;  
Lt. Col. C. L. Beaven, F.A.C.P., (MC), U. S. Army—1 reprint;  
Dr. Louis F. Bishop, Jr., F.A.C.P., New York, N. Y.—2 reprints;  
Dr. Joe P. Bowdoin, F.A.C.P., Atlanta, Ga.—3 bulletins, 1 mimeographed report;  
Dr. Ralph Bowen, F.A.C.P., Oklahoma City, Okla.—1 reprint;  
Dr. Grafton Tyler Brown, F.A.C.P., Washington, D. C.—2 reprints;  
Dr. George H. Coleman, F.A.C.P., Chicago, Ill.—1 reprint;  
Capt. James H. Forsee, F.A.C.P., (MC), U. S. Army—3 reprints;  
Dr. Irving Greenfield (Associate), Brooklyn, N. Y.—3 reprints;  
Dr. F. F. Gundrum, F.A.C.P., Sacramento, Calif.—1 reprint;  
Dr. W. Hiemstra, F.A.C.P., Minneapolis, Minn.—1 reprint;  
Dr. Mendel Jacobi, F.A.C.P., Brooklyn, N. Y.—16 reprints;  
Dr. Jerome G. Kaufman (Associate), Newark, N. J.—1 report of a study, "New Jersey and the Cardiac Child";  
Dr. E. B. Krumbhaar, F.A.C.P., Philadelphia, Pa.—Chapter 8, "Lymphatic Tissue," from "Problems of Ageing: Biological and Medical Aspects";  
Dr. F. LeBlanc (Associate), Elgin, Ill.—1 reprint;  
Dr. George M. Lewis, F.A.C.P., New York, N. Y.—3 reprints;  
Dr. H. R. Litchfield, F. A. C. P., Brooklyn, N. Y.—3 reprints;  
Dr. T. P. Lloyd, F. A. C. P., Shreveport, La.—1 reprint;  
Dr. Charles E. Lyght (Associate), Northfield, Minn.—duplicate copy, "Eighth Annual Report of the Tuberculosis Committee of the American Student Health Association";  
Major H. P. Marvin, F.A.C.P., (MC), U. S. Army—1 reprint;  
Dr. Willard D. Mayer, F.A.C.P., Detroit, Mich.—1 reprint;  
Dr. M. Hill Metz (Associate), Dallas, Tex.—2 reprints;  
Dr. William Gerry Morgan, F.A.C.P., Washington, D. C.—1 reprint and a full series of "Annals of Medical History," January, 1929, to November, 1932;  
Dr. William B. Rawls, F.A.C.P., New York, N. Y.—3 reprints;  
Dr. Ada E. Schweitzer, F.A.C.P., Indianapolis, Ind.—1 reprint;  
Dr. Donald S. Smith (Associate), Pontiac, Mich.—1 reprint;  
Dr. Dudley C. Smith, F.A.C.P., Charlottesville, Va.—8 reprints;  
Dr. Frederick R. Taylor, F.A.C.P., High Point, N. C.—1 reprint;  
Dr. Henry H. Turner, F.A.C.P., Oklahoma City, Okla.—4 reprints;  
Dr. Samuel Weiss, F.A.C.P., New York, N. Y.—3 reprints;  
Dr. Hugh G. Whitehead, Jr. (Associate), Baltimore, Md.—1 reprint;  
Dr. John Zarit (Associate), Denver, Colo.—1 reprint.

## NEW LIFE MEMBER

Dr. Edward L. Tuohy, F.A.C.P., Duluth, Minn., became a Life Member of the College on May 4, 1939.

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Dr. Rock Sleyster, F.A.C.P., and Governor of the College for Wisconsin, was made President of the American Medical Association at its recent annual session at St. Louis.

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Dr. James B. Herrick, F.A.C.P., Chicago, who served for several years on the Board of Regents of the College, was awarded the distinguished service medal of the American Medical Association at its convention in St. Louis on May 15 for his discovery of coronary thrombosis and his contributions toward the cure of heart disease.

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Dr. Edward L. Bortz, F.A.C.P., and Governor of the College for Eastern Pennsylvania, during May was elected to the Presidency of the Philadelphia County Medical Society.

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Dr. D. O. N. Lindberg, F.A.C.P., Medical Director and Superintendent of the Macon County Tuberculosis Sanatorium, Decatur, Ill., was elected President of the Illinois Tuberculosis Association at its annual session, Peoria, April 24-25, 1939.

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Dr. G. Philip Grabfield, F.A.C.P., Boston, has been elected Secretary of the American Society for Pharmacology and Experimental Therapeutics for 1939-40.

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The American Association of Clinical Pathologists, meeting in St. Louis May 13, conferred its Burdick Award, a gold medal given annually for outstanding contribution to medical science, upon Dr. Harry Goldblatt (1938 Phillips medalist of the College), Professor of Experimental Pathology of the School of Medicine and Associate Director of the Institute of Pathology, Western Reserve University, Cleveland. The honor was announced at the convention banquet of the Association, together with citation of Dr. Goldblatt's researches in hypertension and his discoveries of relationships between high blood pressure and diseases of the kidneys.

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Dr. C. H. Cocke, F.A.C.P., Governor of the College for North Carolina, delivered the Lewis Burgin McBrayer address before the North Carolina State Medical Society meeting during May, his subject being "Lewis Burgin McBrayer and the State Sanatorium." This marks the founding of an annual address in honor of the late Dr. Lewis Burgin McBrayer, F.A.C.P., who for many years was the Secretary of the North Carolina State Medical Society and Managing Director of the North Carolina Tuberculosis Association.

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## MEETING OF MARYLAND CHAPTER OF THE COLLEGE

On May 13, 1939, Fellows and Associates of the College residing in Maryland held a sectional meeting at the Maryland Club, Baltimore, for the purpose of receiving reports from those who attended the Annual Session of the College at New Orleans. The Maryland group is organized locally with a president and secretary. Dr. Louis Krause, F.A.C.P., and Dr. W. Halsey Barker (Associate), both of Baltimore, were elected President and Secretary, respectively, for 1939-40. The Maryland members hold two sectional meetings a year, one with a scientific program and social evening

and one almost wholly of a social character, with dinner and reports on College activities.

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CORRECTION—REGISTRATION AT NEW ORLEANS SESSION

In the statement of registration at the recent New Orleans Session of the College, published last month in these columns, the State of Mississippi was inadvertently omitted and the registration for the State of Missouri incorrectly recorded. The corrected figures follow:

	<i>Members</i>	<i>Guest Physicians</i>	<i>Exhibitors</i>	<i>Total</i>
Mississippi .....	14	2		16
Missouri .....	24	3	9	36

The corrected re-capitulation of the total attendance is as follows:

896	Members
525	Guest Physicians
10	Guest Non-Physicians
499	Medical Students
167	Exhibitors
578	Ladies
6	Miscellaneous
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2,681	TOTAL

## MINUTES OF THE BOARD OF REGENTS

New Orleans, La., March 26, 1939

The first meeting of the Board of Regents, held in connection with the Twenty-third Annual Session of the American College of Physicians, occurred on March 26, 1939, at the Municipal Auditorium, New Orleans, La., presided over by President William J. Kerr, with Mr. E. R. Loveland acting as Secretary, and with the following present:

William J. Kerr, *President*  
O. H. Perry Pepper, *President-Elect*  
James B. Herrick, *First Vice-President*  
Charles T. Stone, *Third Vice-President*  
William D. Stroud, *Treasurer*  
George Morris Piersol, *Secretary-General*  
Walter L. Bierring  
James D. Bruce  
Egerton L. Crispin  
James Alex. Miller  
Francis M. Pottenger  
David P. Barr  
Ernest B. Bradley  
Roger I. Lee  
Sydney R. Miller  
Robert A. Cooke  
Ernest E. Irons  
D. Sclater Lewis  
Hugh J. Morgan  
James E. Paullin  
Maurice C. Pincoffs  
Charles H. Cocke

Specially invited guests to this meeting included, from the Committee on Postgraduate Education, Dr. C. Sidney Burwell and Dr. Joseph A. Capps; also Dr. William D. Cutter, Secretary of the Council on Medical Education and Hospitals of the American Medical Association. The only absentees from the Board of Regents were Dr. Noble Wiley Jones and Dr. Walter W. Palmer.

The Executive Secretary read an abstract of the Minutes of the preceding meeting of the Board of Regents, which was approved as read.

Instead of following the regular order of business, President Kerr brought up immediately for discussion the subject of Postgraduate Education, and called upon Dr. Hugh J. Morgan, Chairman of the Committee on Postgraduate Education, to open the discussion, presenting his report and recommendations.

Dr. Morgan first reported upon the recent Postgraduate Courses sponsored by the College at St. Louis, Chicago and Baltimore. A total of 118 attended the Courses, coming from thirty-four different States, from Hawaii and from two Provinces of Canada. Dr. Morgan then proceeded to a report of the activities of his Committee since the last meeting of the Board of Regents. He recalled that in accordance with directions of the Board of Regents at its meeting, December, 1938, two members of the Committee on Postgraduate Education of the College went to Chicago, where they attended a meeting called by Dr. W. C. Rappleye, on the authorization of the Association of American Medical Colleges, to consider the advisability of the formation

of a National Council on Medical Education, Licensure and Hospitals. Dr. Morgan's further report herewith follows:

#### REPORT, COMMITTEE ON POSTGRADUATE EDUCATION

"A meeting was called by Dr. W. C. Rappleye on the authorization of the Association of American Medical Colleges to consider the advisability of forming a National Council on Medical Education, Licensure and Hospitals. The representatives convened in Chicago February 11, 1939. Hugh J. Morgan and Edson W. Carr (alternate; Chicago) represented the College of Physicians.

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"The representatives of the several organizations assembled in Chicago February 11, prior to the annual Congress on Medical Education and Licensure. All of the organizations which had been invited to send representatives did so with the exception of the A. M. A. A letter from Secretary Booth of the Board of Trustees of the A. M. A. was read by Dr. Rappleye, stating that the formal invitation of the Association of American Medical Schools to the Trustees of the A. M. A. was, unfortunately, not delivered to the Trustees. Therefore, the Trustees of the A. M. A. had received no invitation and had appointed no representatives. Dr. Booth stated that the Council on Medical Education and Hospitals had considered the matter and would doubtless be represented. Dr. Wilbur, Chairman of the Council, appeared in the meeting at this point and announced that he represented neither the Council on Medical Education and Hospitals nor the Board of Trustees of the A. M. A. and asked if he might attend as an "unofficial observer." He was welcomed warmly by acting chairman Rappleye.

"The advisability of forming a new organization with wide representation was discussed. It was generally agreed that this was desirable and a resolution was adopted to the effect. The purpose of the organization was defined, by resolution, as follows:

"'The Council is created to meet the need of a body representing the medical profession, the universities, medical schools, hospitals, licensing bodies, specialty boards, public health agencies, and other national organizations in this country which deal with different phases of medical education. The Council shall serve as a clearing house for the coöperative consideration of those problems and programs of professional training with which more than one organization is concerned; as a medium for consultation and mutual assistance in the formulation and support of adequate educational standards; and as an agency for advice and recommendations to member and other organizations dealing with medical education.'

"Many representatives, including those of the College of Physicians, felt that, if this body was to act "as a clearing house for the coöperative consideration" of problems, it was essential that the A. M. A. be represented and take part in the organization of the body (the selection of its name, the writing of its constitution, etc.). Further action was delayed therefore to attend upon the action of the A. M. A. A committee was appointed to confer with the Council on Medical Education and Hospitals to inform them that:

"(1) It is the opinion of the representatives that an advisory board is desirable, to function in the field defined by the resolution;

"(2) The representatives feel it a matter of great importance that the A. M. A., which has through its Council accomplished so much in the field, participate in the organization and administration of such an advisory body.

"The meeting adjourned with the request from the acting chairman that the representatives inform their respective organizations of the action taken and invite endorsement of and participation in the proposed body.



“REPRESENTATIVES APPOINTED TO ATTEND MEETING ON FEBRUARY 11, 1939, TO  
DISCUSS THE PROPOSED NATIONAL COUNCIL ON MEDICAL EDUCATION,  
LICENSURE, AND HOSPITALS

*Association of American Medical Colleges*

William S. Middleton, Madison  
Willard C. Rappleye, New York  
Maurice H. Rees, Denver

*American Hospital Association*

Robin C. Buerki, Chicago  
M. F. Griffin, Cleveland  
Christopher Parnall, Rochester, N. Y.

*The Catholic Hospital Association*

*Federation of State Medical Boards of the U. S. A.*

Walter L. Bierring, Des Moines  
J. W. Bowers, Fort Wayne  
Harold Rypins, Albany

*Advisory Board for Medical Specialties*

Franklin G. Ebaugh, Denver  
John Green, St. Louis  
B. R. Kirklin, Rochester, Minn.

*National Board of Medical Examiners*

Waller S. Leathers, Nashville

*American College of Surgeons*

Arthur W. Allen, Boston  
Dallas B. Phemister, Chicago

*American College of Physicians*

Edson W. Carr, Chicago  
Hugh J. Morgan, Nashville

*Association of American Universities*

E. B. Fred, Madison  
C. S. Yoakum, Ann Arbor

*American Public Health Association*

Waller S. Leathers, Nashville

*American Association for the Advancement of Science, Division of Medical Sciences*

Anton J. Carlson, Chicago (absent) ”

Summarizing his report, Dr. Morgan made the following recommendations:

- (1) That the College of Physicians approve the purpose of an Advisory Council of Education, Licensure and Hospitals, adopted by several organizations, whose representatives met in Chicago on February 11, 1939;

- (2) That two representatives of the College be appointed to attend and participate in the organization meeting and subsequent deliberations of the Advisory Council;
- (3) That our representatives in this Advisory Council state our interest in the subject of graduate training in internal medicine and allied specialties, asking the Council for suggestions as how best to proceed.

President Kerr explained that no positive action on the recommendations was to be taken at this meeting of the Board, but the matter was presented for due consideration and thought from every standpoint. He introduced Dr. William D. Cutter, Secretary of the Council on Medical Education and Hospitals of the American Medical Association, who addressed the Board as follows:

"Mr. President, and members of the Board of Regents, I would like to confirm what Dr. Morgan has already told you about the desire, on the part of the Council on Medical Education, to collaborate with the American College of Physicians and with the American Board of Internal Medicine, insofar as this problem of graduate education in the field of Internal Medicine is concerned. We have seen a very successful illustration of such collaboration carried out in the American Board itself, which is jointly the responsibility of the College and the Section on Medicine of the American Medical Association, and we feel there is every reason to believe, in the light of our experience of the last few years, that such coöperation between the Council and various specialties will prove to be, in the long run, the satisfactory way to deal with problems. It is a fact that a number of the specialty boards, representing specialties, have already tried independently to formulate standards and give approval to different courses in institutions, residencies, etc., in the specialty fields. With some experience of their own, these men are turning to the Council and asking for assistance. We have entered into definite plans of coöperation with the Board of Radiology and Pathology. The people in the field of Ophthalmology and Otolaryngology have expressed a desire to confer with us in regard to plans.

"Perhaps I could make more plain to you what we are talking about if I describe somewhat in detail the plan of collaboration which we have with the Board of Pathology and Radiology. There should be definite means of determining standards of education, training, apprenticeship and other courses which will enter into the training for specializing in these fields. These standards should be formulated by means of conference between representatives of our Council and representatives of specialty societies. The standards and requirements, minimum requirements, were determined and the types of courses to be approved were agreed upon and the Council and specialty group conferred. Collection of information and investigation of hospitals would be better conducted by the Council and its staff, but the plan mentioned is the plan that seemed agreeable to them. After the information was collected, after the institutions were visited and reports made, covering all the points agreed upon as important and essential, we again went into conference with the representatives of the specialty group to determine how that evidence should be evaluated; how courses are to be approved, which approved and which not approved, and then after we reach an agreement in regard to these facts, they are free to publish in any way they see fit, the result of deliberation and equally we will use the channels of publicity of the American Medical Association to make known these institutions and courses acceptable to the specialty groups.

"The reason, I think, why these boards have come to us seeking this form of collaboration is that, in their own experience, they have encountered difficulties. When it is up to a specialty board, for instance, dermatology, to make approval for facilities of graduate training in its field, they do not have a permanent or trained staff of inspection. They depend upon their one board and the members cannot give the proper time to it. A member is asked to visit a few schools in the neighborhood

where he resides and others are asked to make inspection in other regions. There is no uniform inspection or standard. Formulation of opinions are many times influenced by personal factors. For instance, the Board of Otolaryngology and Ophthalmology published a list of residencies recently which they approved. We have published the list we approved. In most part, these lists coincide. There were a few discrepancies which we examined with care to find reasons for discrepancies. I think I can tell you that we have found in every case where these specialty boards have approved institutions which we did not approve, it was because of personal relationship or due to the fact that sufficient time was not taken to go deeply into the situation. On the other hand, where some were approved by us and not by them, we found that this also was due to lack of personal acquaintance with the man at the head of the institution or failure to go deeply into the character of the service. We came to the conclusion, as well as they, that the actual business of making inspection and collecting evidence is better carried out by our staff.

"Another thing, if each one of the specialty boards took up the work of conducting their own investigation there would be a multiplicity of inspection, to which the institutions would rebel. Some of them have expressed dissatisfaction with this condition in which so many different agencies attempt to make investigations, for approval of hospital services and courses of training. So it seems to us that the actual business of collecting information could be better carried out through a single agency, which is already in existence and is familiar with the work. After the information is collected, the Council again confers with the specialty concerned with respect to the evaluation of the evidence. When we have gotten evidence with regard to a service, for instance, dermatology, we sit down with representatives of the board and go over the evidence with them and determine together just exactly which institutions should be approved and which should not be approved. After an agreement is reached about that, we can publish a list with the satisfaction of knowing that the residencies and other courses approved will be acceptable to the specialty societies and specialty boards interested in that field.

"That is the proposal we would like to make to the American College of Physicians. Your Committee, or certain members of the Committee, could consider with us what the essential factors are that go to make up a worth while residency and graduate course in the field of internal medicine. It is not difficult to write an agreement about that. All of the work will go for the same thing, and it will be inevitable that we can arrive at a satisfactory agreement as to what the important elements should be in rating apprenticeships. The kind of training and matters of personnel should be included in the study. Investigation of these institutions, if it meets your approval, can be made when making other investigations. When inspecting a hospital, we can cover all the specialties at one time and submit a report to you concerning evidence which we secure and we can decide what is to be done about it. This sort of collaboration would simplify the work of both organizations. We would not undertake to pass judgment on all the details of specialty training; on the other hand, the public will have greater confidence in this kind of work if not conducted by specialty groups, that might be interested in furthering their own importance and welfare.

"If it is possible for us to join with the College of Physicians in a program of this sort, leading to comprehensive study for graduate study, and proper appraisal of same, in which you yourself will have a part, we shall be very happy indeed to join with you in this kind of enterprise. We hope that we may have the opportunity to discuss this further at a meeting in Chicago, which has been proposed."

In questions and answers following Dr. Cutter's remarks, it was revealed that there is no relationship or plan of coöperation between the work of the Council on Medical Education and Hospitals and the American College of Surgeons. The college of Surgeons has initiated its own independent program of appraisal of educational facilities. It was also revealed that the Council on Medical Education and Hospitals

is composed of seven members, each appointed for a seven-year term. Appointments are made by the President of the American Medical Association. The Council is responsible to the House of Delegates. The Council on Medical Education and Hospitals did not participate in the meeting called by Dr. W. C. Rappleye at Chicago, February 11, 1939, concerning the formation of a National Council on Medical Education, Licensure and Hospitals, only because it had no authority from the House of Delegates of the American Medical Association. It was anticipated that the House of Delegates will issue instructions after its meeting in May of the current year.

Dr. Joseph A. Capps, the other representative of the College at the Rappleye meeting in Chicago, expressed the sentiment that our College should move slowly in the matter and consider many propositions before adopting final action. He pointed out that the new Council is an advisory one and not an executive body, and that our problem is to settle on some agency that can carry to execution the things we require. Dr. Capps said it was self-evident that this should be done by one body, and that if that might be the Council on Medical Education, he thought it would be desirable. Dr. Capps pointed out that two members of the American College of Physicians are already on the Council, and that whereas the present Council members are appointed by the President of the American Medical Association, it would be advantageous to have the By-Laws amended to permit the Council on Medical Education and Hospitals to make nominations, which would later be approved by the House of Delegates.

Dr. Roger I. Lee explained that the Council on Chemistry and Pharmacy of the American Medical Association is a Council of the Board of Trustees of that body, and its members are appointed by the Trustees. The Council on Medical Education and Hospitals is a Council of the House of Delegates. Dr. Lee further deplored the duplication of activity on the part of so many agencies engaging in the same work, pointing out that the American Medical Association conducts a very elaborate survey of hospitals, including the certification of hospitals for internship.

Dr. Ernest E. Irons recommended that the American College of Physicians move slowly and review the possibilities for working with the Council on Medical Education and Hospitals.

Dr. C. Sidney Burwell made two points: first, agreeing that a single body should rate hospitals, and, second, that the problem of graduate education, the problem of training men for the practice of specialties, is an enormously complex one, and that various bodies have gone ahead without sufficient consideration of the ultimate ends. He agreed that the American College of Physicians has a large and proper interest in the matter, and that medical schools have a secondary interest and that the hospitals also have a great interest, because they will be called upon to play a large part. Likewise, licensing boards and public health organizations will be concerned with the problem. Dr. Burwell asked for coordination of all of these interests, and recommended adequate time before reaching a decision on the manner in which the College would participate.

At the request of Dr. Roger I. Lee, Dr. William D. Cutter reported that the Council on Medical Education and Hospitals is made up of the following members:

Dr. Ray Lyman Wilbur, Chairman, San Francisco  
Dr. John H. Musser, New Orleans  
Dr. Fred Moores, Des Moines  
Dr. Reginald Fitz, Boston  
Dr. Fred W. Rankin, Lexington  
Dr. Charles Gordon Heyd, New York  
Dr. F. H. Lahey, Boston  
Dr. William D. Cutter, Chicago

Dr. Cutter explained that the American Medical Association has no other agencies than the Council on Medical Education which are directly concerned with medical

education or the supervision of hospitals. The Association has never assumed responsibility for licensure, because this has been considered a State function and governed by the laws of the several States. The Council on Medical Education, Licensure and Hospitals, proposed by Dr. Rappleye, is to be purely an advisory one, not executive or administrative. It is proposed to be a clearing house for information, for conferences and discussion. It would have no power to control or direct any agencies which have representation in the Council on Medical Education and Hospitals. The field proposed goes no further than the Council on Medical Education and Hospitals, except in the matter of licensure. The Council on Medical Education does not make inspection of medical schools or hospitals except upon invitation.

Dr. Maurice C. Pincoffs inquired if the Council on Medical Education and Hospitals intends to add to its personnel men qualified for making the type of hospital and graduate education survey our College is interested in, or whether the Council is of the opinion that a group of experienced surveyors can survey any field.

Dr. Cutter replied that the Council's investigators would be instructed by special representatives, who would first be informed through advice from the specialty groups. Should this be inadequate, the Council would do the job over again to the satisfaction of the groups interested. Already some of the specialty boards have been invited to send representatives on some of the inspection tours, in order that they may see how the inspections are done and in order that they may instruct the Council how to improve its work. Dr. Cutter explained that no new machinery has yet been set up, but that informal conferences with representatives of interested boards will be arranged. Dr. Cutter also explained that while hospitals are not specifically graded, there are three types of recognition: first, approval for the training of interns; second, approval for training residents for advanced types of education (there are so many specialty fields that some hospitals have many different residencies; a hospital may be approved for some and not other types of residencies); third, admission to the register. This latter includes six thousand hospitals. The admission to the register is done on the basis of correspondence, official reports and investigations by doctors in the locality. The Council has three men who devote themselves exclusively to hospitals; one additional man who devotes his time chiefly to hospitals; and one additional man who devotes his time chiefly to graduate medical education outside of hospitals.

President Kerr discussed the invitation from the Trustees of the American Medical Association for a joint meeting with the Regents of the American College of Physicians, and suggested the possibility of such a meeting being held, at the convenience of the Trustees of the American Medical Association, at Chicago on April 29.

Dr. Hugh J. Morgan, Chairman of the Committee on Postgraduate Education of the College, inquired if our College should merge its interest in support of the Council on Medical Education and Hospitals; insofar as work is concerned in graduate training and medical specialties, could the College do that in a conspicuous fashion? Would it be difficult for the College to do more than simply support and advise with the Council, and would the project in the final analysis be a Council job in the future as in the past? Does the Council on Medical Education and Hospitals feel that specialty training is in its province? Is the American Medical Association, with so many doctors, really concerned with specialty training? Has the American Medical Association been particularly interested in the development of specialties? Have the specialty sections in the American Medical Association been a natural, spontaneous development? Should not specialty training be the natural concern of specialty societies and hospitals, or is it proper that a body dominated by general practitioners should be concerned with specialty training? Would it be reasonable for the College to postpone its decision as to how to proceed in the field of graduate training until after the Advisory Council on Medical Education, Licensure and Hospitals is or-

ganized? Would it be consistent for the College to go into the Advisory Council on one hand and make a decision without consulting the Advisory Council on the other, when the Advisory Council is being formed to act as a clearing house of problems of professional training?

DR. WILLIAM D. CUTTER: "I will be glad to answer these questions. I think we can get further in this intimate discussion.

"I am tremendously interested in this problem and am gratified by the response this afternoon.

"The first question Dr. Morgan asked was whether the part which the College of Physicians would play would be recognized. I think I can say without hesitation that the Council and the American Medical Association would give the fullest publicity to the fact that the College of Physicians had collaborated in this effort. I do not know whether that kind of publicity would be sufficient to be satisfactory from your point of view, but I am certain that by every avenue of publicity we will be glad to call attention to the fact that this is a joint enterprise in which the College has contributed.

"The second question as to whether the American Medical Association, which is an organization of so many doctors, is an organization which, by its very nature can be interested in the problems of the specialties. My answer is unequivocally and emphatically, yes. Medicine is medicine and no part of medicine can exist apart from medicine, and we believe as firmly as we can believe anything, that the American Medical Association is not only interested, but is responsible for every phase of medical activity, including all specialties and insofar as the sections are concerned, they have not been created by means of any force or pressure from the outside. The difficulty we have had is to keep down the number of sections. Many groups demand recognition. Sometimes this recognition has been given and after a few years the meeting dwindled. No effort on the part of the American Medical Association, as a whole, has been made to stimulate the creation of new sections. What we have is the response from the men in special fields."

President Kerr thanked Dr. Cutter for his attending the Regents' meeting and for the information he had furnished, at which time Dr. Cutter retired and the meeting proceeded with the regular order of business.

The Executive Secretary presented the following communications: (1) Dr. Cecil Striker, Cincinnati, Ohio, pointing out a disproportionate ratio of invited guests as against members appearing on the New Orleans program; (2) Dr. Julien E. Benjamin, Cincinnati, Ohio, concerning guest speakers, repetition of speakers on the program of clinics and demonstrations at the New Orleans Session.

Dr. James B. Herrick presented a communication from Dr. Noble Wiley Jones, of Portland, Ore., who was named official representative of this College to attend the inauguration of the Australasian College of Physicians at Sydney, during December, 1938. Dr. Herrick reported that Dr. Jones had attended that meeting, delivered an address and took part in the activities, and received an honorary degree. Dr. Jones had submitted a full report to President Kerr, who, in turn, had submitted it to Dr. Herrick for comment and review. Dr. Jones' five concrete suggestions were read by Dr. Herrick, after explaining that the background for the suggestions was furnished by Dr. Jones being impressed by the importance of keeping in close touch with the English speaking physicians of the world, and feeling that this can be done in several ways. His suggestions follow, with Dr. Herrick's comments indicated in parentheses at the end of each suggestion:

(1) That the American College of Physicians exercise its influence—which would be indirect—to secure Exchange Professorships in medicine and pathology between the Australasian and American Medical Schools. He states that he has met men in Australia whose presence would bring honor to any American school they visited. (I see no objection to this.)

(2) That each year an invitation be extended to an Australasian medical man to take part in our annual session as a guest speaker of the College. As these men are usually full-time workers, on salary, it would be necessary for the American College of Physicians to assume at least part of their expenses. (I think this is all right if he will say "from time to time" instead of each year.)

(3) That the Executive Secretary communicate with the Hon. Secretary of the Royal Australasian College of Physicians each year, six months before the annual meeting of the American College of Physicians, informing him of the date and place of our meeting and invite its members to attend. (Surely no objection to that.)

(4) That an effort on the part of our members be made to attend the annual meetings of the Royal Australasian College of Physicians. They will be repaid many-fold in pleasure, information and a mutual understanding with the Australasian people. (There is no objection to this, I am sure.)

(5) That The American College of Physicians establish an annual prize of a small sum of money, that is, \$100.00, or better \$400.00, to be controlled by the Royal Australasian College of Physicians, and to be presented to a new or recent graduate of any of the medical schools in Australia presenting the best thesis based on original work in medicine or pathology.

Dr. Herrick was not in favor of the last suggestion, because he felt it an artificial way of stimulating men to work, and that it would establish a bad precedent to offer this money as a reward to some young man who presented a thesis, the merits of which would be decided upon by the Australians themselves. He therefore recommended that this suggestion be entirely omitted.

Dr. Herrick went on to state that Dr. Jones had expressed the hope that our College will do everything possible toward entertaining and assisting members of the Royal Australasian College of Physicians when they come to this country. Dr. Herrick expressed the opinion that the Executive Secretary, through the College office, could perform these courtesies, as he has already done in arranging a program and furnishing introductions for one of the Fellows of the Royal Australasian College who is visiting this country this May. Dr. Herrick said that Dr. Jones' report indicated that his mission to Australia had as one of its objectives the establishment of a feeling of goodwill and mutual understanding between members of the two Colleges directly and between the peoples of the two countries indirectly. Dr. Jones had been convinced over many years that it would be important for all English speaking nations to stand together for the preservation of their form of government, their culture and their civilization, and that the people of Australia have the same outlook. Dr. Herrick reported that he had already written to Dr. Jones, expressing the thought that the Regents must be careful in pledging the College in non-professional matters, and that the College ought not to take action along this line. Dr. Herrick recommended that the College thank Dr. Jones for his suggestions and recommendations concerning his visit to the inauguration of the Royal Australasian College of Physicians, and that our Committee on Fellowships and Awards consider the recommendation of offering a prize to any one in the world.

On motion by Dr. Herrick, seconded by Dr. Roger I. Lee, and unanimously carried, it was

RESOLVED, that the recommendations presented by Dr. Herrick be approved.

President Kerr then presented a communication in the form of a telegram and letter from Dr. Olin West of Chicago, inviting the Regents of the American College of Physicians to meet with the Board of Trustees of the American Medical Association for the purpose of discussing a program of graduate education. It was pointed out that the College would be interested only in this particular matter and not in medical economics. The invitation, however, included hospital service, group hos-

pitalization plans, some phases of the problem of economics; the invitation being meant primarily for a joint meeting to talk over common problems between the two organizations. After general discussion, decision on the acceptance of the invitation and the date of the meeting was postponed, until the succeeding meeting of the Board of Regents.

Dr. Sydney R. Miller, Chairman of the Committee on Credentials, presented the report of that Committee in two parts: (1) he distributed a mimeographed list of the candidates for Fellowship and Associateship as recommended for election by the Committee on Credentials on February 26, 1939. There were 43 advancements from Associateship to Fellowship, 10 to be elected directly to Fellowship, 8 deferred for further information and 1 rejected, making a total of 62 candidates for Fellowship that had been acted upon. There were 61 candidates recommended for election to Associateship, 8 deferred and 13 not qualified, making a total of 82 candidates for Associateship that had been acted upon; (2) Dr. Miller then distributed the list of candidates reviewed on the morning of March 26, consisting of (a) 64 candidates for Fellowship, of which 18 were recommended for direct election, 37 were recommended for advancement, 5 were deferred for further credentials and 4 were rejected; (b) 83 candidates for Associateship, of which 2 were recommended for election directly to Fellowship, 70 were recommended for election to Associateship, 6 were deferred and 5 rejected.

Dr. Miller answered questions from the Board of Regents concerning any candidates and explained, where inquiries arose, why candidates were not recommended for election.

On motion by Dr. Sydney R. Miller, seconded by Dr. George Morris Piersol, and regularly carried, it was

RESOLVED, that the following list of 110 candidates be and herewith are elected to Fellowship in the American College of Physicians: (This list was published in the April, 1939, issue of this journal).

On motion by Dr. Sydney R. Miller, seconded by Dr. William D. Stroud, and regularly carried, it was

RESOLVED, that the following list of 131 candidates shall be and are herewith elected to Associateship in the American College of Physicians: (This list was published in the April, 1939, issue of this journal).

On motion by Dr. O. H. Perry Pepper, seconded by Dr. F. M. Pottenger, it was

RESOLVED, that the Chairman of the Committee on Credentials and the Executive Secretary proceed with the revision of the informative booklet concerning criteria for membership and the revision of the proposal form.

In the discussion that followed, Dr. Sydney R. Miller explained that this had been authorized by the Regents at the preceding meeting, but that there had not been adequate time or opportunity to complete the work. The booklet has become obsolete, and it lacks clarity, and it is proposed to thoroughly revise it and improve its appearance.

Dr. James E. Paullin, Chairman of the Committee on Public Relations, presented complaints against a Fellow of the College whose writings in a semi-popular journal were considered derogatory and not in keeping with the dignity and purposes of the American College of Physicians.

The Committee on Public Relations was instructed by the Board of Regents to bring the matter to the attention of this member in an effort to have him desist from this activity, or to present his resignation.



Dr. George Morris Piersol, Secretary-General, reported the following deaths since the last meeting of the Board of Regents, making a total since the last Annual Session of the College of twenty-nine Fellows and four Associates:

*Fellows:*

Berg, Henry W., New York, N. Y., December 22, 1938  
Boettiger, Carl, Flushing, L. I., N. Y., February 1, 1939  
Gregg, Donald, Wellesley, Mass., January 6, 1939  
Kauffman, Lesser, Buffalo, N. Y., March 11, 1939  
Parramore, James Otho, Crown Point, Ind., January 24, 1939  
Stark, Morris, New York, N. Y., July 18, 1935

*Associates:*

Esler, James W., Washington, D. C., December 15, 1938  
Kalteyer, Fred J., Philadelphia, Pa., December 21, 1938

Dr. Piersol then reported the following additional Life Members since the last Regents' meeting in December, 1938:

O. H. Perry Pepper, Philadelphia, Pa.  
Charles Hartwell Cocke, Asheville, N. C.  
Andrew H. Hangarter, Brooklyn, N. Y.  
Richard Arminius Kern, Philadelphia, Pa.  
Edward Bridge Bigelow, Worcester, Mass.  
James B. Herrick, Chicago, Ill.  
William S. Baldwin, Lorain, Ohio  
Lawrence Getz, Ancon, Canal Zone  
Clifford P. Rutledge, Shreveport, La.  
Mortimer Warren, Portland, Maine  
Frank Bethel Cross, Brooklyn, N. Y.  
James Alexander Lyon, Washington, D. C.

At the meeting of the Board of Regents on December 18, 1938, he had reported four Life Members, which makes a total for the year, since the last Annual Session, of 16, or a grand total of 117, of whom 8 have died, leaving a balance of 109 living Life Members.

On motion seconded and unanimously carried, the report of the Secretary-General was accepted.

Dr. Maurice C. Pincoffs made a brief report as the Editor of the ANNALS OF INTERNAL MEDICINE. Due to an increase allowed in his budget, he had been able to add to the office personnel and greatly facilitate the handling of the editorial work of the ANNALS for the future. The circulation of the ANNALS had grown approximately three hundred since the preceding Annual Session, and there has been an ever increasing number of manuscripts presented for publication.

On motion seconded and regularly carried, the report of the Editor was accepted.

Dr. Roger I. Lee, Chairman of the Committee on Future Policy, said that there was no report to be made.

Dr. William D. Stroud, Treasurer, presented the following report:

"As of March 19, 1939, our invested principal in the Endowment Fund was \$68,494.98 in Bonds; our General Fund, \$34,855.50 in Bonds and \$57,390.95 in Stocks, making a total value of \$160,751.43. The book value of that date was \$161,085.00, or a profit on investments of \$333.57. The income on our invested principal is averaging 4 per cent.

"During the past year there has been an increase in the total amount of our Endowment Fund plus our General Fund from \$205,383.47 to \$222,014.12, or a profit

of \$16,630.65 for the year. Our College, therefore, has a cash plus investment value of \$222,000.00, plus the value of our property in Philadelphia."

On motion seconded and regularly carried, the report of the Treasurer was accepted.

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, had no report to present.

Dr. James Alex. Miller, Chairman of the Committee on Finance, reported as follows:

"I have here in the report of the Finance Committee, Mr. President, a detailed account of the investments. I do not think the Regents care for me to read this; however, I will do so if requested. The Finance Committee would like to emphasize again the very excellent financial situation of the College, and particularly in these troublous times that our invested funds have a market value which is definitely more than the cost value. I thought also it would be worth while to read how these are diversified: 65 per cent in bonds; 28 per cent preferred stock; 7 per cent common stock. As to the character of the various investments; public utilities 32 per cent; industrials, both preferred and common, 25 per cent; U. S. Government 17 per cent; railroad 15 per cent; foreign bonds 8 per cent; financial stock 2 per cent; municipal bonds 1 per cent.

"Since the last report to the Board of Regents, the Finance Committee has authorized the purchase of 5,000 Florida Power Corporation, First Mortgage, Series 'C,' 4s, due 1966, at a price of \$4,485.90, for the General Fund; also for the General Fund, 4,000 North American Company, debentures, 3½s, 1949, at a cost of \$4,175.00. For the Endowment Fund, 1,000 North American Company, debentures, 3½s, at a cost of \$1,043.75; also for the Endowment Fund, 1,000 Ohio Public Service, First Mortgage, 4s, 1962, at a cost of \$1,070.00 and 2,000 U. S. Treasury, 2s, 1947, at a cost of \$2,045.75.

"At this present meeting the Finance Committee, as has already been reported by the Treasurer, would report that the Endowment Fund Cost Value is \$68,494.98 and the General Fund Cost Value is \$92,246.45, making a total of invested funds of \$160,741.43. The present market value of these securities, as of March 19, was \$161,085.00, showing a total investment profit, as of that date, of \$333.57. These investments are diversified as follows: Bonds, 65 per cent; preferred stock, 28 per cent, common stocks, 7 per cent. As to the character of the various investments, public utilities, 32 per cent; industrials, both preferred and common, 25 per cent; U. S. Government, 17 per cent; railroad, 15 per cent; foreign bonds, 8 per cent; financial stock, 2 per cent; municipal bonds, 1 per cent.

"At this present meeting, the Finance Committee has authorized the transfer from the General Fund to the Endowment Fund of 3,000 Great Northern, 4s, Series 'H,' convertible, due July 1, 1946, this giving a total of \$5,000.00 of this security in the Endowment Fund. It was voted to sell 5,000 of these Great Northern Bonds, and to buy in their place for the Endowment Fund, 5,000 Great Northern General B, 5½s, due January 1, 1952. This still leaves an uninvested sum in the Endowment Fund of a little less than \$2,000.00.

"For the General Fund there being \$10,000.00 available for investment, it was voted on the recommendation of the Girard Trust Company to buy 40 Shares of the Monsanto Chemical Company, 4½s, cumulative preferred, at an estimated cost of \$4,680.00, and also to buy 40 Shares of the Great Atlantic and Pacific Tea Company, 7 per cent, cumulative preferred, at an approximate cost of \$5,000.00.

"The Finance Committee also voted to recommend to the Board of Regents the adoption of the following resolution:

"RESOLVED, that inasmuch as the Finance Committee reports a most satisfactory

condition of our finances and that this is due very largely to the splendid coöperation and sound recommendations made to it by the Girard Trust Company, through its Trust Investment Department, that the Board of Regents of the American College of Physicians desires to express its deep appreciation of the very efficient service that has been rendered to the College by the Girard Trust Company.

"Finally, the Finance Committee wishes to suggest to the Board of Regents that inasmuch as it has come to the knowledge of this Committee that the present policy concerning commercial exhibits might be modified to the advantage of the College, the Finance Committee would recommend to the Board of Regents that in some suitable manner, possibly through the appointment of a special committee, a thorough study be made in regard to the commercial exhibits, not only from the financial point of view, but also from that of the general interests of the College.

Respectfully submitted,

ROGER I. LEE,  
CHARLES T. STONE,  
WILLIAM D. STROUD,  
JAMES ALEX. MILLER, *Chairman,*  
*Committee on Finance"*

On motion seconded and regularly carried, it was

RESOLVED, that the report of the Finance Committee be accepted; that the recommendation concerning the resolution of thanks to the Investment Counsel, Girard Trust Company, be approved; that the recommendation of the appointment of a special committee to investigate commercial exhibits be referred to the present Committee on Exhibits and Advertising.

The Executive Secretary distributed to all members of the Board of Regents the Auditor's report and detailed financial statements for the year 1938, which herewith follow.

Adjournment:

Attest: E. R. LOVELAND,  
*Executive Secretary*

## MINUTES OF THE BOARD OF REGENTS

New Orleans, La., March 28, 1939

The second meeting of the Board of Regents, held in connection with the Twenty-third Annual Session of the College, was called to order on March 28, 1939, at the Municipal Auditorium, New Orleans, La., with the President, Dr. William J. Kerr, presiding, Mr. E. R. Loveland acting as secretary and with the following present:

William J. Kerr, *President*  
O. H. Perry Pepper, *President-Elect*  
James B. Herrick, *First Vice-President*  
Charles T. Stone, *Third Vice-President*  
William D. Stroud, *Treasurer*  
George Morris Piersol, *Secretary-General*  
Walter L. Bierring  
James D. Bruce  
Egerton L. Crispin  
James Alex. Miller  
Francis M. Pottenger  
David P. Barr  
Ernest B. Bradley

Roger I. Lee  
Sydney R. Miller  
Robert A. Cooke  
Ernest E. Irons  
D. Sclater Lewis  
Hugh J. Morgan  
James E. Paullin  
Maurice C. Pincoffs  
Charles H. Cocke

Abstracted Minutes of the preceding meeting of the Board of Regents were read and approved.

Dr. James E. Paullin, Chairman of the Committee on Public Relations, presented and recommended the acceptance of the resignations of Dr. William Riley Brooksher (Fellow), Fort Smith, Ark., and Major Alfred Mordecai (Associate), (MC), U. S. Army.

On motion by Dr. Paullin, seconded by Dr. Stroud, it was

RESOLVED, that the resignations of Dr. William Riley Brooksher (Fellow) and Major Alfred Mordecai (Associate) be accepted.

Dr. Paullin then reviewed four cases affecting fees and dues. A resolution was adopted providing for the waiver of dues until recovery and resumption of practice in the case of those men who were out of practice because of illness, in accordance with provisions of the By-Laws.

Dr. Sydney R. Miller, Chairman of the Committee on Credentials, continued his earlier report, reading Article IV, paragraph 2, of the Constitution, calling particular attention to the phrase, "and such additional rules as the Board of Regents may from time to time adopt": "(a) Fellows. Fellows shall be members of the medical profession engaged as practitioners, teachers or research workers in Internal Medicine, or in an allied specialty, who shall have been elected in accordance with the By-Laws and such additional rules as the Board of Regents may from time to time adopt—the By-Laws and such additional rules being intended to insure the election only of internists of such high qualifications, personal and professional, as would entitle them to be rated as fully qualified Fellows. Fellows shall be authorized to use the letters F.A.C.P. after their names on professional cards, in professional directories and in professional publications. Fellows shall have the right to vote and to hold office." Under the authority given the Regents by this section, the Credentials Committee recommended the following new rule for the advancement of Associates to Fellows: "No Associate hereinafter elected shall be eligible for consideration for Fellowship unless he or she shall have been certified by one of the American Boards for the certification of specialties." Dr. Miller pointed out that most of the specialties have certifying boards, such as those in Radiology, Pediatrics, etc. Dr. Miller pointed out that this proposal is not presented as an amendment, but that the Constitution already makes provision for additional rules and regulations adopted by the Regents.

Dr. Roger I. Lee inquired whether it might not be advisable to modify such a rule so that it would not be absolute, pointing out that there might be exceptions, that some men might not want to spend the time or money to be certified as an internist, since certification might not be of material advantage to some.

President Kerr pointed out that this new rule would not in any way alter the provision already in the Constitution and By-Laws for the admission of men directly to Fellowship who present adequate and exceptional qualifications. The proposed rule would apply only to Associates elected hereafter, and would provide a definite standard of accomplishment, professionally, during the five-year Associate term, but that mere certification in itself might not guarantee advancement to Fellowship, because the College has other requirements.

Dr. James Alex. Miller expressed sympathy with the project in mind, but indicated a hesitancy in voting for it at present. He said in part: "It is fundamentally not exactly the kind of rule that was in mind when this opportunity was offered to give the Regents extra powers. It is a fundamental change. In the next place, I wonder if we are ready to make this radical step at the present time. Thirdly, I would like to suggest that this has definite relation to our financial structure. That ought to be considered, too. I think it is a valuable thing to be brought up, and I think we ought to think it over carefully. Perhaps, it is better not to take immediate action on it, but have it brought up later as an amendment to the By-Laws, to come before the College as a body. I am in sympathy with the plan."

DR. GEORGE MORRIS PIERSOL: "This proposal does not involve the status of present Associates. Only those elected in the future would be subject to this rule. Our present standards are not sufficiently definite. The Credentials Committee after years of struggle has been searching to find some adequate and proper yardstick to evaluate the professional standards of Fellowship. The ones at present are certainly inadequate. They have little virtue. They are absolutely not adequate criteria. This College was instrumental in setting up the American Board of Internal Medicine. The fundamental plan of certification is sound, and we were instrumental in initiating this policy, and now have a controlling hand in this Board. It seems ridiculous, after having created this and having it in operation, for us to circumvent its requirements and follow inferior standards ourselves. The Committee feels that until such a plan as this proposal is adopted, we shall never arrive at an adequate basis for determining professional qualifications. After considerable thought and deliberation, this recommendation was submitted. It does not affect the present method of electing Associates. It does make it obvious that there shall be certain things Associates shall have to do before being considered for Fellowship. It does not imply that if the Associate passes the certifying board he will be elected a Fellow, for there are other qualifications, if the By-Laws still remain. The Committee feels very strongly about this and believes it will be a proper step."

At the request of Dr. O. H. Perry Pepper, Dr. Walter L. Bierring, Chairman of the American Board of Internal Medicine, stated that the adoption of the proposed regulation by the College would not conflict in any manner with the age or time limitations already prescribed in the By-Laws of the College, or those of the American Board of Internal Medicine.

Dr. Pepper pointed out that it is planned to republish the requirements for certification by the American Board of Internal Medicine, because the rules are now read differently by some than by others. He proposed that the Credentials Committee of the College and the By-Laws Committee of the Board might well discuss the matter together and have the proposed action correlated.

Dr. James B. Herrick proposed that final action might be deferred until the next meeting of the Regents, and President Kerr asked the Credentials Committee to confer with the Board of Internal Medicine and re-present the question in December, 1939.

Dr. Sydney R. Miller, continuing his report, pointed out that the Credentials Committee, in preparation for the revision of the informative booklet concerning requirements, send a copy of the booklet with a letter to every Regent and Governor, requesting a careful study and making suggestions for constructive changes to be considered and consolidated by the Committee. He pointed out that this might serve as a wide basis of opinion on which to base not only the changes suggested, but perhaps, other revisions.

Dr. David P. Barr, Chairman of the Committee on Fellowships and Awards, reported that Dr. Jonathan C. Meakins had recommended that inasmuch as Dr. Kenneth Austin Evelyn desired to pursue a further year as an Assistant Resident, the Research Fellowship awarded him as of July 1, 1939, be delayed until July 1, 1940. Dr. Barr recommended that the Research Fellowship be so delayed.

On motion by Dr. Barr, seconded by Dr. O. H. Perry Pepper, and regularly carried, it was

RESOLVED, that the Research Fellowship awarded Dr. Kenneth Austin Evelyn, at his request, be delayed until July 1, 1940.

Dr. Walter L. Bierring made the following report for the American Board of Internal Medicine:

"On behalf of the American Board of Internal Medicine, I wish to give only a brief report, a report of progress in the methods and procedure of certification. Certification without examination is gradually becoming limited to very exceptional cases. Certification by examination is comprising a larger group of applications. In the written section examinations held in October and February, two hundred and sixty-five appeared for examination at different centers throughout the country and Canada. Failures comprised approximately 15 per cent. There appeared in this Session the largest number of candidates for a practical examination, 75, and of these, 19 failed; 20 or 25 per cent. Certain changes are being made in the requirements, and it is hoped that there may also be a coördination with the requirements of this College and other certifying boards or agencies. There have been some changes in the official family. Dr. Ernest E. Irons has been selected as Chairman, Dr. Reginald Fitz as Vice-Chairman and Dr. William S. Middleton as Secretary."

On motion by Dr. Bierring, seconded by Dr. O. H. Perry Pepper, and regularly carried, it was

RESOLVED, that the Board of Regents of the American College of Physicians shall reappoint Dr. David P. Barr to succeed himself as a representative of this College on the American Board of Internal Medicine for the term expiring 1942.

On inquiry from Dr. Sydney R. Miller, Dr. Walter L. Bierring explained that if a candidate fails in the written examination he cannot appear for reëxamination for a period of two years; if failing in the practical examination, he may re-appear in one year.

Dr. James Alex. Miller, Chairman of the Committee on Finance, reported as follows: "This is the report of the Committee which was appointed at the December, 1938, meeting of the Regents to consider dues and initiation fees. I was appointed Chairman of a special Committee with power to select other members. Dr. Paullin and Dr. Stroud served as the other members. This Committee has reviewed with care the statement of income and analyzed its sources, showing that approximately 35 per cent of the College income is from dues and 17 per cent is from initiation fees. Both dues and initiation fees have been reduced 25 per cent in recent years. The various projects proposed by the College, both for the future and in operation at present, lead the Committee to recommend that there be no change in dues at this time, but the Committee also recommends to the Board of Regents that it authorize, through a suitable committee, a careful study of our income and expenditures, both as they exist at present and particularly as to how they should be planned for the future, and that the factors above enumerated, as well as others that will undoubtedly suggest themselves, be considered by such a committee, and that a report be rendered to the Board of Regents."

On motion by Dr. James Alex. Miller, seconded and regularly carried, the above report was accepted.

In further commenting on the resolution above adopted, Dr. James Alex. Miller pointed out that an analysis as proposed will involve matters under the jurisdiction of various committees, such as the Committee on Exhibits and Advertisements, Committee on Future Policy, the Committee on Fellowships and Awards and the Committee on Postgraduate Education. He pointed out that there are many items that need

review, not simply by the Finance Committee, but by all the factors which are represented here, which have to do particularly with future policies. There has been some discussion of altering the commercial exhibits, from which we have received a net profit varying from six to fourteen thousand dollars, according to the place of meeting. He pointed out also that there has been an increasing amount of expenditures for the annual meetings; that there have been suggestions for an increase in the Endowment Fund. Dr. Miller felt that these issues should be intelligently and intensively studied. He recommended that the President and the President-Elect will bear in mind the appointment of those who are capable of facing this whole question of the financial future, from the standpoint of these considerations.

On further motion by Dr. James Alex. Miller, seconded and regularly carried, it was

RESOLVED, that the action taken at the last meeting of the Board of Regents be rescinded in respect to a committee to confer with the Committee on Commercial Exhibits, and that the special committee of investigation be authorized to act in this capacity.

The special committee of investigation of fees and dues was discharged with the thanks of the College.

President Kerr brought up the matter of the joint meeting between the College and the American Medical Association, and reported that Secretary Olin West of the American Medical Association had suggested the possibility of the meeting being held on the last Saturday in April, between the Regents of the College and the Trustees of the American Medical Association.

Dr. Kerr reported that he had discussed with Dr. West the question of other problems that Dr. West had proposed for discussion, and had told him that this College would not feel we were prepared to take up economic or other problems outside of the field of graduate or postgraduate education. Dr. West had stated that he would bring this to the attention of the Board of Trustees, and assured Dr. Kerr that the subject of postgraduate training would be the chief topic of discussion.

Dr. O. H. Perry Pepper recommended that the so-called Liaison Committee, which had been appointed some years ago to confer with a similar committee of the American College of Surgeons, be suspended, because it does not serve as an executive committee and also because the College already has a multiplicity of committees, the duties of which are not well defined. Dr. Pepper suggested that more responsibility might properly be turned over to the present Executive Committee, and thus simplify our structure.

President Kerr, pointing out that the Liaison Committee is not an official committee, declared it suspended.

The Secretary, Mr. Loveland, presented a list of six Associates and five Fellows, whose dues were delinquent two or more years, and who, according to the By-Laws, should be dropped from the Roster. The list had been presented to the Board of Governors for review, so that each Governor might have an opportunity to make suggestions or recommendations.

On motion by Dr. Barr, seconded by Dr. Paullin, and regularly carried, it was

RESOLVED, that the delinquent Fellows and Associates shall be dropped from the Roster of the College at the end of sixty days from this meeting, unless they shall have in the meantime satisfied the provisions of the By-Laws with regard to payment of their dues.

The Secretary, Mr. Loveland, then presented the list of Associates elected at the 1934 Annual Session, whose maximum five-year term had expired without their

meeting the requirements for Fellowship. An analysis of the 1934 class of Associates showed the following results:

Advanced to Fellowship .....	79 (82.3%)
Credentials not presented .....	11 (11.5%)
Credentials presented, but inadequate for election .....	3 ( 3.1%)
Previously dropped or resigned .....	3 ( 3.1%)
Total, Associates elected, 1934 .....	96

In accordance with the By-Laws, those Associates who had not presented their credentials, or credentials had been found inadequate, totalling 14, were discontinued on the Associateship Roster.

The Secretary, Mr. Loveland, presented an inquiry from the College Governor for Florida, Dr. Turner Z. Cason, concerning the presentation of candidates for membership from Cuba. Dr. Cason, if authorized by the Board of Regents, would endorse these candidates for membership, but unfortunately they were not acquainted or connected in the United States, and have no acquaintanceships among Fellows of the College who may act as their proposers and seconders.

In the discussion that followed, it was brought out that the College has previously gone on record as not encouraging the proposal of candidates from any country unless they speak English, and thus may receive some direct benefits through the journal, the Annual Sessions and other activities of the College. It was further brought out that there would be an undue responsibility given to the Credentials Committee to select the pioneer members of the College from the Island of Cuba, if these men shall be totally unknown to any who are already Fellows of the College.

On motion by Dr. Pincoffs, seconded by Dr. Paullin, it was

RESOLVED, that there be no special action setting aside the present provisions of the By-Laws to enable candidates from Cuba to be presented for membership.

Dr. Charles H. Cocke, Chairman of the Board of Governors, reported upon the proceedings of that body at its meeting on March 27, including: (1) discussion of the question of commercial exhibits, responsibility for which rests in the hands of a Committee appointed by the Board of Regents; (2) Governor Henry M. Thomas, Jr., of Maryland, had suggested that the Board of Regents appoint a committee or director to supervise, organize and correlate the postgraduate courses offered by the College, so that scheduled courses shall not be dropped in the future; further that this committee shall collect data to find out the wishes of the membership with regard to courses desired, suitable time of the year, etc. Dr. Cocke had suggested to individual Governors that they canvass members in their territory who attended the various postgraduate courses of the College, after the list has been furnished by the Executive Secretary, in an attempt to secure such additional information. The findings of the Governors will be submitted to the Committee on Postgraduate Education. The question of location of courses, the Governors felt, should be carefully studied, because it plays such an important part in the popularity of courses; (3) the Governors felt it important that announcement of time and place of postgraduate courses should be made early, so that members may make plans, financially and professionally, in time to attend.

Dr. O. H. Perry Pepper suggested that the Board of Governors may be the best agency through which to appoint a committee for this investigation, the Governors being closer to the membership.

On motion by Dr. Pepper, seconded and regularly carried, it was

RESOLVED, that the Board of Regents request the Board of Governors to appoint a committee or chairman for the purpose of carrying out investigation of the postgraduate courses as they deem best.



Dr. Pepper pointed out, after the adoption of the motion, that this new committee will merely be an advisory committee to furnish data to the present Committee on Postgraduate Education.

Dr. O. H. Perry Pepper reported that on the list of the Board of Directors of the Gorgas Memorial Institute, the name of Dr. James H. Means appears as a representative of the American College of Physicians. Dr. Pepper had been notified that his name would appear on the next list. Dr. Pepper asked the Board if the College desires to be represented. Such representation implies responsibility and approval of that body.

On motion by Dr. Pepper, seconded and regularly carried, it was

RESOLVED, that the question as to whether the American College of Physicians shall be officially represented on the Board of Directors of the Gorgas Memorial Institute shall be left over for consideration at a later meeting.

DR. WILLIAM J. KERR: "I should like to say that this is the last meeting of the Board of Regents over which I shall preside, and I want to take this opportunity to thank you all for the opportunity to work with you and to work on the program and do the other things pertaining to the office. I am glad I had a year of preparation for this, but the year just coming to a close has been of tremendous interest and of educational value to me, and I am grateful for the honor and opportunity. There is something else very close to my heart. I notice, in plans to come before the College on Thursday, recommendations of the Nominating Committee, following the rules of the College, indicate that there are certain ones who have been with us a great many years, the names of which will no longer be on the active list of Officers or Regents. Four of our most distinguished men in American medicine will no longer be on this list. Dr. Pottenger, particularly, has been on the Board longer than anyone else. Dr. Herrick, Dr. Bierring and Dr. James Alex. Miller have been on many years, and have given excellent and remarkable service, and I think that the College is losing from its active list the remarkable work of these men, although I know we shall always be able to turn to them for help and advice. When we adjourn today, we do so in affection to these men."

Adjournment:

Attest: E. R. LOVELAND,  
*Executive Secretary*

## MINUTES OF THE BOARD OF REGENTS

New Orleans, La., March 31, 1939

The third meeting of the Board of Regents, held in connection with the Twenty-third Annual Session of the College, was called to order on March 31, 1939, at the Municipal Auditorium, New Orleans, La., with the newly inducted President, Dr. O. H. Perry Pepper, presiding, with Mr. E. R. Loveland acting as secretary, and with the following present:

O. H. Perry Pepper, *President*  
William D. Stroud, *Treasurer*  
George Morris Piersol, *Secretary-General*  
Ernest B. Bradley  
Robert A. Cooke  
D. Sclater Lewis  
Hugh J. Morgan  
Francis G. Blake  
William J. Kerr

Charles T. Stone  
Maurice C. Pincoffs  
Charles H. Cocke

The secretary read abstracted Minutes of the preceding meeting of the Board of Regents, which were approved as read.

The Secretary was called upon to present invitations for the 1940 Session of the College. For 1940 he presented invitations from Rochester, N. Y.; San Francisco, Calif.; St. Paul, Minn.; Buffalo, N. Y.; Cleveland, Ohio and Boston, Mass. For 1941, he presented an invitation from Kansas City, Mo. The invitations from Rochester and Buffalo were primarily civic ones, coming from the local Chambers of Commerce. The interest of the Board was primarily focused, for geographic reasons, on the invitations from Cleveland and Boston, and, therefore, these invitations were read in detail. They included official letters not only from the civic bodies, but from the Deans of the Medical Schools, the local medical societies, civic authorities, and others. Dr. William J. Kerr explained that the invitation from San Francisco would be continued for the future, and he withdrew the invitation for current consideration. Inasmuch as Dr. Vernon Rowland and Mr. Mark Egan were present as representatives from Cleveland, they were called upon to present in more detail the facilities available.

DR. VERNON ROWLAND: "As a representative of the Cleveland profession and the Academy of Medicine, I am authorized to extend a cordial and official invitation from Cleveland. It has been twelve years since the College met there. Cleveland's renewed invitation was in last year, and there has been increasing interest since then. You are already familiar with the Lakeside Hospital group in Cleveland; its staff will give full coöperation, as will also that of the Children's Hospital. We have a large City Hospital with over three thousand beds, with all branches of service. There is a tuberculosis and chest surgery clinic. Also, there are a group of private hospitals. The American Medical Association will convene in Cleveland in 1941, and since the College meeting is overdue, we think 1940 would be the right time for this meeting in Cleveland. We have all the physical equipment necessary. There is a new public hall for the exhibits and the General Sessions. Its music hall, seating three thousand, is very popular, artistic and acoustically perfect. There are facilities for round tables and small group meetings. The public hall is offered free of all charge to the College; in addition, the services of the Convention Bureau and their corps of helpers, as well as free time on the radio, if desired, will be available. The auditorium is within walking distance from the downtown hotels.

"There are adequate hotel facilities, and I can guarantee eight or nine hundred rooms, or more, at the time of the College meeting. The Cleveland Hotel is under the same roof as the Terminal Station, which is the center of transportation. It has a huge garage, and is almost a town in itself. The Statler Hotel is also located within walking distance of the auditorium, and offers splendid facilities.

"As to location, Cleveland is centrally located, and on all transportation lines. In general, we think we have the clinical facilities and physical equipment necessary, and we believe wide interest and full coöperation will be at your disposal. It would be particularly timely for the College to come to Cleveland in 1940, as the American Medical Association will meet there in 1941. We feel your meeting with us is overdue. I wish to assure you that if the Board decides to accept this invitation, Cleveland will give its best efforts and time."

MR. MARK EGAN: "Mr. President and members of the Board of Regents, I have nothing to add particularly, but I did want to be here to let you know that we mean to coöperate with your headquarters and your local committees. I think Dr. Rowland has mentioned everything, unless you have questions to ask. We can furnish a fine place for exhibits, and we call your attention to the fact that you will be able to

proceed to the meeting rooms from the exhibit hall. There are eight meeting rooms under one roof, and ample meeting facilities."

Answering an inquiry by Dr. Charles H. Cocke, Dr. Rowland stated that the most appropriate dates would be the last week in March or the first week in April, 1940, both of these dates being open.

President Pepper then called upon Dr. James H. Means to submit the invitation from Boston.

DR. JAMES H. MEANS: "Mr. President, I have come here at your invitation. I am authorized to speak for no one but myself. You already have the letters of invitation from our Boston institutions and organizations. I shall be glad to answer any questions; I can speak for my own clinic, saying that we shall be happy to entertain the members of the College in 1940, or any other year. I spent a day with the Executive Secretary looking over the facilities in Boston. They are nothing like they are in Cleveland, but the clinical facilities are good. We have medical schools and a number of hospitals, and all of these, I am sure, would like for you to come to Boston. There are two Regents and one Governor from Boston, each of whom has joined the invitation."

On inquiry by Dr. Pincoffs, Dr. Means replied that while Boston would prefer having the College in 1940, it would welcome the College in 1941 or any other year.

President Pepper thanked Dr. Means, Dr. Rowland and Mr. Egan for coming and presenting the invitations, but said that discussion and decision would be deferred until later on the agenda, whereupon Drs. Means and Rowland and Mr. Egan retired.

Dr. William J. Kerr reported that he had exchanged telegrams with Dr. Olin West of the American Medical Association concerning the joint meeting of our Regents and the American Medical Association Trustees.

On motion by Dr. Kerr, seconded by Dr. Charles T. Stone, and regularly carried it was

RESOLVED, that the full Board of Regents of the American College of Physicians accept the invitation of the Trustees of the American Medical Association to hold a joint meeting at the American Medical Association's headquarters in Chicago on Saturday, April 29; further RESOLVED, that the necessary expenses of the Regents for attendance at this meeting shall be borne by the College.

It was pointed out that our Board of Regents may hold a meeting of its own at the Drake Hotel, Chicago, after the joint session with the Trustees of the American Medical Association is over. Details were left to the Executive Secretary and the President.

The next order of business concerned a decision as to whether the College should have representation on the Advisory Council on Education, Licensure and Hospitals.

DR. HUGH J. MORGAN: "Mr. Chairman, the Committee on Postgraduate Education recommends that the College approve the formation of this Advisory Council, and shall appoint two representatives from the College, these representatives to be instructed to bring before the Council our problems in postgraduate training for discussion and for such advice as this Council will deem wise to give. I think it would be a logical thing for the College to have such representation, if this Council is coming into being. There is no doubt that interested organizations are going to join this Council. The idea of such a Council is a reasonable and sound one, and I think no harm will be done by attempts that this Council may make in the field of graduate education."

On motion by Dr. Morgan, seconded by Dr. William D. Stroud, and regularly carried, it was

RESOLVED, that the American College of Physicians shall accept the invitation to appoint two representatives on the Advisory Council on Medical Education, Licensure and Hospitals, and that these two representatives shall be appointed by the President.

Thereafter, President Pepper appointed as the College representatives, Dr. Hugh J. Morgan and Dr. James H. Means.

The next order of business was the election of the Treasurer, Secretary-General, Executive Committee and the appointment of other standing committees.

On motion by Dr. M. C. Pincoffs, seconded by Dr. William J. Kerr, and unanimously carried, Dr. William D. Stroud was reelected as Treasurer of the College.

On motion by Dr. Charles H. Cocke, seconded by Dr. Ernest B. Bradley, and unanimously carried, Dr. George Morris Piersol was reelected Secretary-General.

For the Executive Committee, Dr. M. C. Pincoffs nominated Dr. Reginald Fitz; Dr. George Morris Piersol nominated for reelection Dr. Roger I. Lee, Dr. Hugh J. Morgan and Dr. M. C. Pincoffs. The nominations were seconded by Dr. William D. Stroud. Dr. George Morris Piersol nominated Dr. Ernest B. Bradley, the motion being seconded by Dr. Charles H. Cocke. A motion was made, seconded and carried that the nominations be closed, and that the secretary cast the ballot; therefore, the personnel of the Executive Committee for 1939-40, the President, President-Elect, Treasurer and Secretary-General being members ex officio, consists of the following:

#### EXECUTIVE COMMITTEE, 1939-40

O. H. Perry Pepper, *Chairman*  
James D. Bruce  
George Morris Piersol  
William D. Stroud  
Ernest B. Bradley  
Reginald Fitz  
Roger I. Lee  
Hugh J. Morgan  
Maurice C. Pincoffs

On motion by Dr. William J. Kerr, seconded by Dr. Charles H. Cocke, and regularly carried, Dr. Sydney R. Miller was re-nominated as a member of the Committee on Credentials from the Board of Regents for an additional year, until 1940, to coincide with his term as a Regent. President Pepper requested Dr. Miller to continue serving as Chairman of the Credentials Committee.

Dr. Charles H. Cocke, Chairman of the Board of Governors, reported that Dr. J. Owsley Manier, of Nashville, had been reappointed on the Committee on Credentials for the term ending 1942. The full personnel of the Committee on Credentials for 1939-40 is as follows:

#### COMMITTEE ON CREDENTIALS, 1939-40

Sydney R. Miller, <i>Chairman</i>	(1940)	} —from the Board of Regents
George Morris Piersol	(1940)	
Ernest B. Bradley	(1941)	
<hr/>		
J. Owsley Manier	(1942)	} —from the Board of Governors
William B. Breed	(1940)	
Charles H. Cocke	(1941)	

President Pepper reported that according to rules and regulations of the Board of Regents, it was the President's duty to appoint members of several committees,

list of which he read. Before making any appointments, he opened discussion as to the advisability of continuing the present Committee on Future Policy for the Development of Internal Medicine, which has been in existence since 1936. He pointed out that the duties of a new investigative committee very closely duplicate the duties of the Committee on Future Policy.

After general discussion and review of the work of the Committee on Future Policy, Dr. William D. Stroud moved, and Dr. Ernest B. Bradley seconded the motion as follows, which motion was regularly adopted:

RESOLVED, that the present Committee on Future Policy be abolished with thanks, and that the President be empowered to appoint a Special Committee on Survey and Future Policy, consisting of five members to be appointed annually by the President for one year, these members not necessarily selected from the Board of Regents.

In further discussion, it was suggested that this Special Committee on Survey and Future Policy be composed of the Chairmen of several of the more important Committees, such as the Finance Committee, Committee on Credentials, the Editor, the Committee on Exhibits and Advertising and the American Board of Internal Medicine.

President Pepper called to the attention of the Regents that according to the regulations, the Regents appointed the members of only two committees, while the President appoints the members of eleven committees. Some of these committees are appointed without limit; some for one year and some for more than one year; furthermore, that the original motions are not specific as to whether committee members shall be appointed from the Board of Regents or from the membership-at-large, and that frequently appointments from the Board of Regents for terms of two or more years may extend beyond a Regent's term on the Board. In many ways, Dr. Pepper thought it desirable to make use of the Regents and Governors and members-at-large on the committees, and suggested the possibility of a study of committee structure before the next autumn meeting of the Board. He suggested that the Executive Secretary and the President make a study of the situation and draw up some suggestions in this regard.

On motion by Dr. Ernest B. Bradley, seconded by Dr. William D. Stroud, and regularly carried, it was

RESOLVED, that the President be instructed to report at the next autumn meeting recommendations on the qualifications, personnel and tenure of office of committees.

President Pepper reported that he had received the resignation of Dr. Walter E. Vest as Governor for West Virginia. In accordance with the By-Laws, President Pepper appointed to succeed Dr. Vest, Dr. Albert H. Hoge, of Bluefield, W. Va., to serve until the next regular election.

On motion by Dr. Charles H. Cocke, seconded and regularly carried, it was

RESOLVED, that the regrets of the Board of Regents be sent to Dr. Walter E. Vest.

The next order of business was final action on the 1940 meeting place, and President Pepper requested the Executive Secretary to report upon his inspection trips to Boston and to Cleveland.

Mr. Loveland in his report pointed out that in company with Dr. Means, he had recently inspected all possible places for the meeting in Boston, but that none of the halls seemed entirely acceptable, with the result that if the Annual Session of the College shall be held in Boston, it would have to be held in the Statler Hotel. While this hotel has better facilities for the meeting of the College than other places in Boston, it nevertheless had the limitations of a ballroom that would seat not more than fifteen hundred individuals, and very limited space for the exhibits. Space for

round tables would be limited to three rooms a day, with a maximum attendance from 100 to 125 in each. Boston's clinical facilities were excellent; its physical facilities limited.

Mr. Loveland reported that Cleveland has a public auditorium with excellent physical arrangements for the meetings, exhibits, round tables and other features. Both cities have adequate hotel accommodations for as many as would be attending the College Session.

Mr. Loveland also reported that the Board of Governors had unanimously adopted a resolution recommending to the Board of Regents that Cleveland's invitation be accepted for 1940.

The conditions existing in both Boston and Cleveland were discussed at length, whereupon Dr. Hugh J. Morgan moved and Dr. William J. Kerr seconded the following resolution, which was unanimously passed:

RESOLVED, that the 1940 Annual Session of the College shall be held in Cleveland.

Thereafter followed discussion of the appointment of a General Chairman. On motion by Dr. Piersol, seconded by Dr. Cocke, and unanimously carried, it was

RESOLVED, that Dr. Howard T. Karsner, of Cleveland, be elected General Chairman of the 1940 Session.

On motion by Dr. Bradley, seconded and regularly carried, it was

RESOLVED, that the selection of the date of the 1940 Session be left to the President, General Chairman and Executive Secretary.

Dr. Charles H. Cocke reported from the Board of Governors the personnel of that Board's Committee to undertake the investigation and survey of postgraduate courses as follows:

\*Dr. Henry M. Thomas, Jr., Baltimore, Md.  
Dr. Edward L. Bortz, Philadelphia, Pa.  
Dr. James G. Carr, Chicago, Ill.  
Dr. James J. Waring, Denver, Colo.  
Dr. Ernest H. Falconer, San Francisco, Calif.

On motion by Dr. Hugh J. Morgan, seconded and regularly carried, it was

RESOLVED, that the Executive Secretary express the great appreciation of the College, through the Regents, to all those who participated in arranging and carrying out the Postgraduate Courses in various cities preceding the New Orleans Session.

Dr. Maurice C. Pincoffs made the following suggestions in connection with meetings of the Board of Regents:

- (1) that the Board of Regents, following each Regents' meeting, receive a mimeographed copy of the full Minutes;
- (2) in advance of each meeting of the Board of Regents, a brief synopsis of the main agenda of the forthcoming meeting be sent to each Regent, so that he may give topics some preliminary thought and consideration;
- (3) when a topic of major importance is coming up, a special meeting of the Regents should be held with that as the only topic, rather than having any time given over to routine matters.

Dr. Hugh J. Morgan reported that the American College of Surgeons one year ago had invited the American College of Physicians to work in the field of graduate education. No action had yet been taken in regard to that invitation; and, as the Col-

\* Chairman.

lege of Surgeons had been informed that action had been deferred previously, they were looking to this meeting for a decision.

Inasmuch as the Regents had decided to defer action still further, Dr. Morgan proposed that it might be appropriate for our President to write to the American College of Surgeons, informing them that action has been deferred, and that our College is going into the Advisory Council on Medical Education, Licensure and Hospitals to discuss this matter further.

President Pepper expressed the opinion that it is unfortunate that some matters of the greatest importance are left to the Friday meeting of the Board of Regents at the Annual Sessions. These meetings are more sparsely attended than those earlier in the week. He, therefore, suggested that more important matters be scheduled for preliminary discussion and action earlier in the week, probably at the Tuesday meeting. He suggested that instead of scheduling the midweek meeting of the Regents at the noon hour, that a regular morning or afternoon be set aside, so that all important business could be attended to earlier in the week. He felt that members of the Board could sacrifice their scientific interest in the program for that period, and that those making the program should list none of the Regents for the morning or afternoon of this important meeting.

President Pepper announced his appointments to standing and special committees for 1939-40. A list of these committees and members thereof appears in the May, 1939, issue of this journal.

Adjournment:

Attest: E. R. LOVELAND,  
*Executive Secretary*

## MINUTES OF THE GENERAL BUSINESS MEETING

New Orleans, La., March 30, 1939

The Annual Business Meeting of Fellows and Masters of the American College of Physicians was held in the Municipal Auditorium, New Orleans, at 4:45 p.m., March 30, 1939, with the President, Dr. William J. Kerr, presiding and the Executive Secretary, Mr. E. R. Loveland, acting as Secretary.

The Minutes of the preceding Annual Business Meeting were read by the Secretary and approved.

President Kerr reviewed the activities of the College during the past year, referring especially to the increase in the diversity of the activities as each year passes. He pointed out that this has given evidence of more specific purpose in the activities of the College and that the initiation of Postgraduate Courses had been of considerable significance. The College had been actively studying the possibility of developing more work in graduate education for men planning to enter the special fields of medicine. He prophesied an extension of the activities of the College in the future and complimented the work accomplished in the executive offices of the College. He extended his appreciation to the Officers, Committees, Regents and Governors, and the Credentials Committee in particular, for the remarkable work they had done during the year. He expressed pleasure in working with Dr. John H. Musser, General Chairman of the New Orleans meeting, in connection with the Twenty-third Annual Session. An effort had been made to bring before the College the very best that could be obtained from all parts of the United States, Canada and Mexico. Approximately three hundred and fifty titles and speakers had been made available on the program, through the General Sessions, Special Lectures, Round Tables, Dry Clinics and hospital Clinics.

In the absence of Dr. William D. Stroud, Treasurer, President Kerr announced that the finances of the College were in excellent shape, that the Finance Committee and the Treasurer had been diligent in their work, and that full details of the Treasurer's annual report would appear in the "Annals of Internal Medicine."

Mr. E. R. Loveland presented the following annual report of the Executive Secretary:

"The proceedings of this meeting, especially those of the Board of Governors and Board of Regents, will be published in the 'Annals of Internal Medicine.' The meeting city for 1940 will be determined by the Board of Regents at its meeting tomorrow. The invitations most seriously under consideration come from Boston and Cleveland.

"The College accounts, according to our universal custom, have been audited by a certified public accountant, and all the statements have been presented and approved by the Finance Committee and the Board of Regents. Through the coöperation of the President, of the Treasurer and of the Secretary-General, as well as other Officers, Regents and Governors of the College, and with the help of a competent staff, the work in the Executive Offices of the College has been carried on with as great dispatch, promptness and efficiency as possible. The Board of Regents authorized the appointment of an assistant to the Executive Secretary at its meeting in December, 1938, and thereafter in consultation with the President-Elect, Secretary-General and the Treasurer, Mr. Lee Russell Hegland was appointed early in February. Mr. Hegland is a graduate of the Wharton School of the University of Pennsylvania and has had a number of years experience before joining our staff. The annual amount of correspondence and details of the Executive Offices has made it utterly impossible



for your Executive Secretary to carry on without assistance. This help and consideration extended by the Regents has been deeply appreciated. It is the aim of your Executive Offices to extend every help and every possible courtesy to the members at all times. We have splendid facilities at our headquarters in Philadelphia, and we wish again to remind you that you are always welcome to visit us.

"The Twenty-third Annual Session of the College in New Orleans has been a most successful and well attended meeting. The President, the General Chairman, the local committees through their chairman, the Convention Bureau, the hotels, the Auditorium staff and the Ladies' Entertainment Committee have done an excellent job, and we appreciate the coöperation and assistance they have given us. Our general registration was 1,574 with 571 visiting ladies, making a total of 2,145."

Dr. George Morris Piersol presented the following annual report of the Secretary-General:

DR. PIERSOL: "Since the last Annual Session of this College, the membership report shows that only five Fellows and three Associates have been dropped for delinquency; the resignations of three Fellows and three Associates have been accepted; four Associates and twenty-nine Fellows have been lost by death; and twenty-two Associates were dropped for failure to qualify for Fellowship in the maximum five-year period, as prescribed by the By-Laws. This year 228 were elected to Fellowship, the vast majority of whom were advancements from Associateship. 204 have been elected to Associateship.

"Sixteen Fellows have become Life Members since the last Annual Session, making a total of one hundred and seventeen on the Life Membership scroll. Eight of these Life Members are deceased, leaving one hundred and nine.

"The total membership of the College is now constituted as follows:

Masters .....	2
Fellows .....	3,027
Associates .....	1,202
	<hr/>
	4,231 TOTAL

"The Committee on Postgraduate Education arranged a number of intensive postgraduate courses immediately preceding the opening of this Session. Admission to the courses was restricted to members of the College and those attempting to qualify for membership or for advancement to Fellowship. Two courses were given at Johns Hopkins University and the University of Maryland at Baltimore, one in General Medicine and one in Cardiovascular and Respiratory Diseases. One course was given at Northwestern University, Chicago, in Cardio-Renal-Vascular Medicine; two courses were given at Washington University, St. Louis, one in Cardiovascular Diseases and one in Diseases of the Glands of Internal Secretion. The total registration for these courses numbered about 125, the registrants coming from various parts of the United States and Canada. It is hoped that with the further coöperation of the Governors, this important activity of the College will continue to increase in interest and scope."

DR. PIERSOL: "Mr. President, in the past year, during which you have so ably and wisely guided the destiny of this College, you have become more than ever endeared to all who have had the privilege of working with you. We are deeply appreciative of the never-failing spirit of coöperation and courtesy that has marked all our associations.

"Therefore, on behalf of the Officers, Regents and Governors of the American College of Physicians, I have the honor to present you with this Gavel, an enduring

symbol of the high office which you have held, as well as a token of our affection and esteem."

DR. KERR: "Dr. Piersol, Fellows and Associates, I cannot say that I did not know there was going to be a Gavel presented because I have, upon previous occasions, seen this same thing done, but not until two years ago, on a similar platform, did I have the slightest idea I would be the recipient of such a Gavel. I would like to say only this; that I never have enjoyed two years more in anything I have done in association with my colleagues in this country, and I am very grateful for the honor you have done me. The fellowship in this organization is something superior and I believe it is leading American medicine in the right direction. I thank you from the bottom of my heart.

"It now gives me the very greatest of pleasure to ask two of our distinguished Officers and Fellows to escort the new President to the platform. I am going to ask Dr. Morris Piersol, from the great city of Brotherly Love, Philadelphia, and my fellow Californian, Dr. Francis Pottenger, to escort Dr. Pepper to the platform.

"Dr. Pepper, the destinies of the College are in your hands."

DR. O. H. PERRY PEPPER: "Mr. Chairman, Fellows and Associates, it is hard to believe that two years have passed since I attended the ceremony at which the same thing that is happening to me, happened to Dr. Kerr. It has been very instructive and interesting to watch the College grow under Dr. Kerr's leadership. I can only hope that two years from now I can retire with as clear a conscience.

"The Presidency of the American College of Physicians is a great honor and I assure you that I deeply appreciate it and I shall strive to do all within my power to serve the College faithfully and efficiently, and to continue the successful administration of Dr. Kerr.

"The Officers of the College, its Regents and Governors are merely representatives of the membership, chosen directly or indirectly, to act as a machinery to carry on the business and government of the College, just as Congress does that of the nation.

"There is, however, one great difference—we, the Officers of the College,—receive no mandate on any subject. We did no electioneering and so had no platform and made no promises—possible or impossible.

"This leaves us, of course, freer than Congressmen to do what we think is right, but it also makes it harder for us to know just what our constituents want us to do and we have to decide ourselves what is best for the College.

"In doing this, we need your help; we need the expression of your opinion. And it seems to me that district meetings, such as the very successful one recently held in Philadelphia, under the leadership of Governor Bortz, in addition to being pleasant and useful occasions, offer an excellent opportunity for a free discussion of the activities and objectives of our College; the conclusions being later reported by the Governor to the Board of Governors and Board of Regents. Do you want the College to reduce its activities and cut the dues? Do you want to embark on new activities which might demand more funds? Some of the suggestions which have reached me have certainly fallen into this latter class—for example, the survey of hospitals for internships, residencies and graduate training, or again a survey of public health facilities in the cities of this country.

"Or should we merely increase our present activities as finances and opportunity permit? Should we study the problem of tuberculosis in medical students and interns? Should we try to reduce the cost of medical textbooks? Should we start a golf tournament at our meetings? These latter are mentioned merely to stress the fact that there is nothing that you may not want to discuss.

"But before you crystallize your views concerning the activities and objectives

of the College, you should have clearly in mind the facts of the case, so that you will not be making suggestions which are beyond the possibilities of the College as it now exists. Let me point out that our College is still very young. Like the young, it is tempted to admire and to try to emulate the older and bigger boys.

"Our College has a membership of about 4,200, including Fellows and Associates; the College of Surgeons has over 13,000 Fellows alone; the American Medical Association over 100,000.

"Our College has a gross annual income of about \$90,000.00; the College of Surgeons has almost five times as much; while the American Medical Association has a profit from its journal alone about seven times greater than our gross income.

"Our dues are \$15.00, our initiation fee, \$80.00; the College of Surgeons' dues are \$25.00 a year, with an initiation fee of \$100.00. Our members receive the 'Annals' free, but the Fellows of the American College of Surgeons have to pay the subscription for 'Surgery, Gynecology and Obstetrics.'

"We are not only young, but still poor and humble. Our headquarters are small and simple, but adequate; only those of you who have seen the buildings of the College of Surgeons and of the American Medical Association can properly compare the three.

"In presenting these comparisons, I am not belittling our College—far to the contrary—for I sincerely admire the steady, healthy growth of our activities during the past years, and it seems to me that the achievements and activities of our College form a very creditable list. Our annual meetings have been increasingly successful and certainly accomplish their purpose of bringing together the pick of the internists of this country and Canada. I can picture no more valuable meeting than ours, with its general sessions, clinics, round table discussions and lectures, not to mention the opportunities for personal exchange of ideas off the meeting floor. I have already mentioned the district meetings, which have been successfully held in several States during the past few years.

"For the past two years, the College has organized the pre-meeting refresher courses, which is another step along the line of offering facilities for graduate education. This is a new activity of the College and may well grow very greatly in the future.

"Next I should mention the journal of the College, the 'Annals of Internal Medicine.' This fine journal has grown steadily to its present size. New departments have been added to it, and there is no reason to think that it will not continue to increase as time goes on and finances make it possible.

"In its meetings and refresher courses and the 'Annals,' the College is encouraging graduate education, and in a small way it is also playing a part in developing graduate training for recent graduates. This year the College granted three Research Fellowships for selected men to continue their work after finishing their internships and commencing their research field. This is graduate training of the best type and is also a contribution towards medical research. The Phillips Award is another item and, as you know, is a reward for research accomplishment. Also, the College has, in coöperation with the American Medical Association, initiated within the past few years the American Board of Internal Medicine, which is another step taken to raise standards of medical practice and to encourage postgraduate training and postgraduate education. Our activities in graduate training are just commencing while the College of Surgeons spends annually in this field alone about as much as our total annual income. Last winter we conferred with the College of Surgeons on these matters; and next month our Regents are to hold a similar meeting with the Trustees of the American Medical Association.

"Now it seems to me that this is a remarkably fine record, and I, as a member of the College, am proud of the record of the College and naturally as an Officer of the College, I am proud to be an Officer, but also I feel deeply the responsibility of

helping to continue the advances which the College has made. However, there is the danger of our College trying to move too fast, trying to undertake too much for its present age, size and income.

"Now obviously the most popular program for a politically minded President to offer is more service and less taxes. Unfortunately, for me, I am so sincerely impressed with what our College has done and is doing today, that I believe our chief need is to move slowly and, as we said in the war, 'to consolidate our position.'

"As institutions go our College is still very young and I for one seldom advise the use of growth hormones in boys who seem perhaps a trifle slow in growth. Usually they go on their normal course and catch up when the puberty spurt of growth takes place. This is a far healthier program for boys, and so it seems to me it is for our College. Let us be ourselves—go our own way, develop our own character and personality. No testosterone for us! Let us admire the College of Surgeons, the American Medical Association, the Association of American Physicians and other organizations, but let us not feel we must copy each of them. Let us respect their several special fields of activity, and leave to them those things that are more appropriate for them than for us.

"In this manner, it seems to me, our College can best serve its members and carry out the purposes for which it was founded as stated in Section I, Article III of our Constitution:

'The object of the American College of Physicians shall be to establish an organization composed of qualified internists of high standing who shall meet from time to time for the purpose of considering and discussing medical and scientific topics, and who through their organization shall attempt to accomplish the further purposes of: (a) maintaining and advancing the highest possible standards in medical education, medical practice and clinical research; (b) perpetuating the history and best traditions of medicine and medical ethics, and (c) maintaining both the dignity and the efficiency of Internal Medicine in its relationship to public welfare.'

President Pepper called for the report of the Committee on Nominations, which, in the absence of the Chairman, Dr. James Alex. Miller, was presented by Dr. D. Sclater Lewis, a member of this Committee.

DR. LEWIS: "Mr. President, in accordance with the By-Laws, Article I, Section 2, we present the following report of the Nominating Committee:

"(A) *For the Elective Offices:*

*President-Elect* ..... James D. Bruce, Ann Arbor, Mich.  
*First Vice President* ..... Allen A. Jones, Buffalo, N. Y.  
*Second Vice President* ..... Gerald B. Webb, Colorado Springs, Colo.  
*Third Vice President* ..... J. Morrison Hutcheson, Richmond, Va.

This list of nominees has been duly published in the 'ANNALS OF INTERNAL MEDICINE' at least one month before the present date.

"(B) *For the Board of Regents:*

*Term Expiring 1942*

Charles T. Stone, Galveston, Tex.  
 Reginald Fitz, Boston, Mass.  
 Egerton L. Crispin, Los Angeles, Calif.  
 Francis G. Blake, New Haven, Conn.  
 William J. Kerr, San Francisco, Calif.

" (C) *For the Board of Governors:*

*Term Expiring 1941*

Charles H. Turkington .....CONNECTICUT—Litchfield

*Term Expiring 1942*

Oliver C. Melson .....ARKANSAS—Little Rock  
 Ernest H. Falconer .....NORTHERN CALIFORNIA—San Francisco  
 Fred M. Smith .....IOWA—Iowa City  
 Joseph E. Knighton .....LOUISIANA—Shreveport  
 Henry R. Carstens .....MICHIGAN—Detroit  
 Edgar van Nuys Allen .....MINNESOTA—Rochester  
 A. Comingo Griffith .....MISSOURI—Kansas City  
 Robert B. Kerr .....NEW HAMPSHIRE—Manchester  
 George H. Lathrope .....NEW JERSEY—Newark  
 Charles H. Cocke .....NORTH CAROLINA—Asheville  
 Julius O. Arnson .....NORTH DAKOTA—Bismarck  
 Alexander M. Burgess .....RHODE ISLAND—Providence  
 Kenneth M. Lynch .....SOUTH CAROLINA—Charleston  
 Paul K. French .....VERMONT—Burlington  
 Walter B. Martin .....VIRGINIA—Norfolk  
 Charles E. Watts .....WASHINGTON—Seattle  
 Walter E. Vest .....WEST VIRGINIA—Huntington  
 Hugh A. Farris .....MARITIME PROVINCES—St. John, Canada  
 Charles F. Moffatt .....QUEBEC—Montreal, Canada

Respectfully submitted,

DR. D. SCLATER LEWIS,  
 DR. HENRY M. THOMAS, JR.,  
 DR. FRED W. WILKERSON,  
 DR. DONALD J. FRICK,  
 DR. JAMES ALEX. MILLER, *Chairman,*  
*Committee on Nominations."*

President Pepper then called for any nominations that might be made from the floor. In the absence of any such nominations from the floor, motion was made, seconded and regularly carried, that it be

RESOLVED, that nominations be closed and that the Executive Secretary be instructed to cast a unanimous ballot.

The Secretary declared all nominees presented by the Committee on Nominations elected.

At this point, President Pepper requested Dr. Francis M. Pottenger and Dr. George Morris Piersol to conduct to the platform, the President-Elect, Dr. James D. Bruce, Ann Arbor, Michigan.

On motion by Dr. C. W. Dowden, seconded and unanimously carried, it was

RESOLVED, that the cordial thanks of the American College of Physicians be extended to the Retiring President, Dr. William J. Kerr; to the General Chairman, Dr. John H. Musser; and to the chairmen and members of his various committees, individually and collectively, for their faithful work in the preparation and conduct of the New Orleans Session; to the Ladies Entertainment Committee for their efficiency, hospitality and courteous entertainment of our ladies; to the medical schools and hospitals of New Orleans for putting their facilities at the disposal of the College,

and for their helpful participation; to the New Orleans Association of Commerce and its officers for their assistance; to the New Orleans Municipal Auditorium and its staff for exceptional coöperation and help; to the Roosevelt and Jung Hotels for their assistance and aid in providing for our entertainment and comfort.

On motion by Dr. Allan Eustis, seconded and unanimously carried, it was

RESOLVED, that a special vote of thanks be extended through Mr. Edgar Rea, Manager of the Municipal Auditorium, to all employees under him for their uniform, efficient coöperation during the Convention, and especially to Mr. Bourda for his arrangement of the lighting in the Auditorium.

Adjournment:

Attest: E. R. LOVELAND,  
*Executive Secretary*

## THE AMERICAN COLLEGE OF PHYSICIANS

### EXECUTIVE SECRETARY'S FINANCIAL REPORT

1938

The Auditor's report of his examination of the accounts of the College is hereto attached. The activities of the College are growing rapidly from year to year, but increased income from the annual exhibits, advertising in the "ANNALS OF INTERNAL MEDICINE" and a gradual growth in membership preserves a satisfactory credit balance, as indicated by a total balance of \$16,630.65, of which \$4,021.98 was added to the Endowment Fund and \$12,600.67 was added to the General Fund.

1935 Balance .....	\$17,182.09	1937 Balance .....	\$23,765.75
1936 " .....	24,946.53	1938 " .....	16,630.65

Due to a change in accounting policy, which more clearly sets out the true financial condition of the College, only a proportion of the subscription receipts for Volume XII, "ANNALS OF INTERNAL MEDICINE" (July, 1938, to June, 1939), have been credited to 1938, the balance being reserved to cover expenses of publication of the last six numbers (January to June, 1939) of the journal. During previous years the entire subscription receipts were credited to the current year, and, therefore, to make the 1938 balance comparable with the balances of preceding years above recorded, \$13,723.24 should be added to the 1938 figure.

The total principals of the two Funds on December 31, 1938, were:

Endowment Fund .....	\$ 68,564.25
General Fund .....	153,449.87
	<u>\$222,014.12</u>

Although no liquidating dividends were received during 1938 from the banks in Pittsburgh that closed during the depression, and in which there remains a balance of \$5,709.33, we are assured of some dividends during 1939. It is probable that the College will never collect the full balance from these closed banks, but it has been totally impossible to determine or estimate what proportion of the balance will eventually be paid.

Attention is called to the recommendation of the Auditor that a proportion of the investments in the General Fund, represented by bonds, be transferred to the Endowment Fund, because it seems improbable that these funds will be required in the General Fund and because these investments are functioning generally as endowment funds already.

Due to materially increased income from subscriptions and advertising in the "ANNALS OF INTERNAL MEDICINE," Volume XI, which was completed with the June, 1938, Issue, showed a surplus of \$6,678.86, in spite of the fact that this volume contained about four hundred more pages than any preceding Volume of the journal.

While the expenses for conducting the Twenty-second Annual Session in New York City during 1938 were considerably in excess of those for any preceding meeting, the income from exhibits and guest fees was very much larger than from any preceding meeting, with the result that there was a credit balance of \$2,126.88.

Page 14 shows a summary of the budgets approved by the Board of Regents on December 18, 1938, for the year 1939; to wit, a total estimated income of \$98,100.00 and total estimated expenditures of \$77,875.00, with an estimated balance of \$20,225.00.

Respectfully submitted,

(Signed) E. R. LOVELAND,  
*Executive Secretary*

March 1, 1939.

H. I. MACLEAN

309 Valley Road

Llanerch, Pa.

February 28, 1939

To the Board of Regents  
American College of Physicians, Inc.  
Philadelphia, Pa.

*Mr. E. R. Loveland, Executive Secretary*

*Dear Sirs:*

I have examined the accounts of the

AMERICAN COLLEGE OF PHYSICIANS, INC.

for the year ended December 31, 1938, and the accompanying statements, including the Balance Sheet at December 31, 1938, the analyses of the General Fund and the Endowment Fund and the Detailed Statement of Operations for the year ended December 31, 1938, are in accordance with the books of account and in my opinion set forth correctly the financial position at December 31, 1938, and the results of operations for the calendar year ended December 31, 1938, subject to the following comments:

*Cash:* The cash was properly accounted for. The following is a statement of the cash in the various depositories:

Girard Trust Company, Philadelphia .....	\$6,260.69
Provident Trust Company, Philadelphia .....	861.47
Royal Bank of Canada, Montreal .....	1,005.80
	<u>\$8,127.96</u>

*Accounts Receivable:* The accounts receivable were examined and found to be less than one year old and appear to be good and collectible. The detailed accounts receivable were in agreement with the control account. No requests for confirmation of the accounts were mailed.

*Investments:* The securities were accounted for by direct correspondence and the income for the period under review was verified.

*Deferred Claims:* The amount of the deferred claims, representing the funds due from the receivers of closed banks is as follows:

	<i>Balance Dec. 31, 1938</i>
Bank of Pittsburgh, Pittsburgh .....	\$1,461.97
Exchange National Bank, Pittsburgh .....	1,166.14
Highland National Bank, Pittsburgh .....	3,081.22
	<u>\$5,709.33</u>

It is noted that no liquidating dividends were received during 1938, and it is, therefore, suggested that the accounts be reviewed in order to determine the amount that may be paid upon final liquidation and the accounts adjusted accordingly.

*General Fund:* The book value of the investments of the General Fund at December 31, 1938, amounted to \$92,186.30, and it is noted that such investments are held principally for the purpose of yielding income for the College rather than for current operating purposes. Inasmuch as these investments are functioning generally as endowment funds, it is recommended that the College consider the advisability of a transfer from the General Fund to the principal of the Endowment Fund, or to classify such an amount as may not be required for current operations to another classification which may be called Funds Functioning as Endowment. Such an action would enable the current financial position of the College to be more clearly stated.

*General:* The increase in the amount of the Endowment Fund and the General Fund during the year 1938 is as follows:

	<i>Balance Jan. 1, 1938</i>	<i>Net Increase</i>	<i>Balance Dec. 31, 1938</i>
Endowment Fund .....	\$ 64,534.27	\$ 4,029.98	\$ 68,564.25
General Fund .....	140,849.20	12,600.67	153,449.87
	<u>\$205,383.47</u>	<u>\$16,630.65</u>	<u>\$222,014.12</u>

In accordance with the instructions of the Executive Secretary, the subscription account of Volume XII of the ANNALS OF INTERNAL MEDICINE was adjusted so as to include only the estimated amount of income applicable to the operations for the year based on the number of issues published for which printing costs had been incurred to December 31, 1938. The prepaid insurance at December 31, 1938, was not set up as a deferred expense; the other deferred and accrued items were verified; the charges to the College Headquarters account were examined, and in my opinion appear to be proper charges to this account; the charges to the Furniture and Equipment accounts represent proper additions to this account and the allowance for depreciation appears to be adequate; a depreciation reserve account has been set up for the new building in accordance with the action of the Board of Regents at the meeting on December 12, 1937, which provided that depreciation on the building should be taken into account at the rate of \$1,000.00 per year; the footings and extensions of the inventory were verified; in accordance with the action of the Board of Regents at the meeting on December 12, 1937, a reserve fund of \$2,000.00 has been set up in order to amortize the cost of the Directory over a two year period; all ascertainable liabilities have been included in the balance sheet; all recorded receipts from dues, initiation fees, exhibits, advertising, sales of publications, etc., were properly deposited in bank and all disbursements, as indicated by the vouchers, cancelled checks and bank statements, were properly recorded in the books of account.

Very truly yours,

(Signed) H. I. MACLEAN,  
Certified Public Accountant



AMERICAN COLLEGE OF PHYSICIANS, INC.

Balance Sheet, December 31, 1938

<i>General Fund</i>		<i>Liabilities</i>	
<i>Assets</i>			
Cash in banks and on hand.....	\$ 7,174.14	Accounts Payable.....	\$ 73.00
Accounts Receivable:		Deferred Income:	
Advertising.....	\$ 818.56	Advance Subscriptions, ANNALS OF	
Hornblower and Weeks.....	37.04	MEDICINE.....	14,270.86
		23rd Annual Session, Exhibit.....	2,014.69
Inventory of Keys, Pledges and Frames, at cost.....		Directory Publication Reserve Fund.....	2,000.00
Accrued Income on General Fund Investments.....			
Accrued Income on Endowment Fund Investments,			
Due to General Fund.....	742.70		
Investments at Book Value.....	92,186.30		
Insurance Deposit.....	555.00		
Deferred Expenses, 23rd Annual Session.....	2,611.69		
Deferred Claims:			
Banks in process of liquidation:			
Bank of Pittsburgh.....	\$ 1,461.97	General Fund, as annexed.....	153,449.87
Exchange National Bank, Pitts-			
burgh.....	1,166.14		
Highland National Bank, Pitts-			
burgh.....	3,081.22		
College Headquarters, Real Estate.....	57,728.45		
Less, Allowance for Depreciation.....	2,000.00		
Furniture and Equipment, at cost.....	9,565.85		
Less, Allowance for Depreciation.....	4,352.69		
	<u>\$171,808.42</u>		<u>\$171,808.42</u>
<i>Endowment Fund</i>			
Cash in Banks.....	\$ 1,153.82	Endowment Fund, Principal.....	\$ 68,564.25
Accrued Interest.....	742.70	Accrued Income, Due General Fund.....	742.70
Investments at Book Value.....	67,410.43		
	<u>\$ 69,306.95</u>		<u>\$ 69,306.95</u>
	<u>\$241,115.37</u>	TOTAL LIABILITIES AND FUNDS.....	<u>\$241,115.37</u>
TOTAL ASSETS.....			

## GENERAL FUND

For the Year Ended December 31, 1938

Balance, January 1, 1938.....	\$140,849.20
Less:	
Transfer to Endowment Fund of the Initiation Fees of Life Members.....	1,070.00
Summary of Operations for the Year ended December 31, 1938:	<u>\$139,779.20</u>

*Income:*

Annual Dues.....	\$26,339.77	
Initiation Fees.....	13,925.00	
Subscriptions, ANNALS OF INTERNAL MEDICINE..	12,667.38	
Advertising, ANNALS OF INTERNAL MEDICINE...	9,592.95	
Income from Invested Funds, General.....	3,063.07	
Income from Invested Funds, Endowment.....	2,616.65	
Exhibits, 22nd Annual Session.....	13,442.20	
Guest Fees, 22nd Annual Session.....	745.00	
Round Tables, net, 22nd Annual Session.....	196.68	
Profit on Keys, Pledges and Frames.....	143.21	
Dividend on Perpetual Insurance Deposit.....	60.00	
Annals of Clinical Medicine.....	14.60	
Total Income.....		\$82,806.51

*Expenses:*

Salaries.....	\$20,854.42	
Postage, Telephone and Telegraph.....	3,678.99	
Office Supplies and Stationery.....	1,313.35	
Printing.....	20,815.29	
Traveling Expenses.....	4,687.77	
College Headquarters:		
Maintenance.....	\$2,422.83	
Taxes.....	1,168.75	
Insurance.....	179.03	3,770.61
Directory Publication Reserve Fund.....	2,000.00	
Loss on Sale of Investments, General Fund.....	2,031.71	
Depreciation on Building, Furniture and Equip- ment.....		1,788.42
Grant to Commission on Graduate Medical Edu- cation.....		100.00
Postgraduate Courses, net.....	566.15	
John Phillips Memorial Prize.....	107.01	
Research Fellowships.....	3,006.71	
Other Expenses:		
22nd Annual Session.....	\$3,124.24	
ANNALS OF INTERNAL MEDICINE..	439.24	
Miscellaneous.....	851.93	4,415.41
Total Expenses.....		<u>\$69,135.84</u>
Net Income for the Year Ended December 31, 1938.....		13,670.67
Balance, December 31, 1938.....		<u><u>\$153,449.87</u></u>

## ENDOWMENT FUND

For the Year Ended December 31, 1938

Principal Account, January 1, 1938.....	\$64,534.27
Add:	
Life Membership Fees received during 1938.....	\$3,066.00
Transfer of Initiation Fees of New Life Members from General Fund.....	1,070.00
	<u>4,136.00</u>
	\$68,670.27
Deduct:	
Loss on Sale of Investments.....	106.02
Principal Account, December 31, 1938.....	<u>\$68,564.25</u>
Income Account:	
Income from Investments earned during 1938.....	\$ 2,616.65
Deduct:	
Research Fellowships.....	\$3,006.71
John Phillips Memorial Prize.....	107.01
Excess of Expenses over Income, charged to General Fund Operations for 1938	<u><u>\$ 497.07</u></u>

## INVESTMENTS

December 31, 1938

<i>Par Value</i>	<i>Bonds</i>	<i>Endowment Fund Invest- ments</i>	<i>General Fund Invest- ments</i>
\$ 4,000	Appalachian Electric Power Co., Deb., 4½s, 1948.....	\$ 4,140.00	
5,000	Bell Telephone of Canada, 5s, 1955.....	5,562.50	
2,000	Canadian Nat'l (West Indies) SS. Co., Ltd., 5s, 1955.....	2,040.00	
5,000	Columbia Gas & Electric Corp., Deb., 5s, 1961.....		\$ 4,956.25
5,000	Commonwealth Edison Co., 1st Series "F," 4s, 1981.....	4,744.35	
5,000	Florida Power Corp., 1st Mort., Series "C," 4s, 1966.....		4,485.90
5,000	Government of Dominion of Canada, 4s, 1960	4,662.50	
2,000	Great Northern Railway Co., Series "H," 4s, 1946.....	2,100.45	
3,000	Great Northern Railway Co., Series "H," 4s, 1946.....		2,910.45
5,000	New York Central RR, 3¾s, 1946.....	4,900.00	
1,000	North American Edison Co., Deb., Series "A," 5s, 1957.....	1,032.75	
4,000	North American Edison Co., Deb., Series "A," 5s, 1957.....		4,114.85
5,000	Northern States Power Co., 1st & Ref. Mort., 3½s, 1967.....	4,806.25	
2,000	Ohio Edison Co., 1st Mort., 4s, 1965.....	2,115.00	
3,000	Ohio Edison Co., 1st Mort., 4s, 1965.....		3,172.50
5,000	Pennsylvania RR, Gen., 4¼s, Series "E," 1984.....		5,013.10
2,000	Port of New York Authority, Interstate Bridge, 4½s, Series "B," 1952.....	2,042.20	
2,000	Port of New York Authority, Interstate Tunnel, 4¼s, Series "E," 1958.....	2,065.40	
5,000	Southern Pacific Co., 3¾s, 1946.....		5,008.65
5,000	Texas & Pacific Ry. Gen. & Ref., Series "B," 5s, 1977.....	5,313.40	
2,000	U. S. Treasury, 4s, 1954.....	1,998.13	
20,000	U. S. Treasury, 3¼s, 1945.....	19,887.50	
5,000	Virginia Public Service, 5½s, 1946.....		5,133.65
<u>\$102,000</u>	<u>TOTAL, Bonds.....</u>	<u>\$67,410.43</u>	<u>\$34,795.35</u>
			<u>\$102,205.78</u>

*Shares**Stocks*

50	American Brake Shoe & Foundry Co., Conv., Pfd.....	\$ 6,163.60
50	American Gas & Electric Co., \$6.00, Pfd....	5,537.25
50	Atchison, Topeka & Santa Fe, 5%, Pfd....	4,970.75
50	Caterpillar Tractor, 5%, Pfd.....	5,103.55
100	Chase Nat'l Bank of New York.....	4,550.00
50	Continental Can Co., \$4.50, Cum. Pfd.....	5,125.00
50	E. I. du Pont, 6%, Cum., Deb.....	6,899.00
20	J. C. Penney Co.....	1,375.30
50	Johns-Manville Corp., 7%, Cum. Pfd.....	6,326.10
150	Pacific Gas & Electric Co., 6%, Pfd.....	4,640.50
50	Timken Roller Bearing Co.....	3,407.25
50	Union Carbide & Carbon Corp.....	3,292.65
	<u>TOTAL, Stocks.....</u>	<u>\$57,390.95</u>
	<u>TOTAL, Investments.....</u>	<u>\$67,410.43</u>
		<u>\$92,186.30</u>
		<u>\$159,596.73</u>

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